11-1-1996

Catalyzed additions to alkene double bonds: (I) Fumarase-catalyzed hydration of alkene double bonds (II) Alumina-catalyzed hydrochlorination of alkene double bonds

Charles Francavilla

CATALYZED ADDITIONS TO ALKENE DOUBLE BONDS:
(I) FUMARASE-CATALYZED HYDRATION OF ALKENE DOUBLE BONDS
(II) ALUMINA-CATALYZED HYDROCHLORINATION OF ALKENE DOUBLE BONDS

by

CHARLES FRANCAVILLA

NOVEMBER 1996

THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE

APPROVED:

Terence C. Morrill
Project Advisor

G. A. Takacs
Department Head

Rochester Institute of Technology
Rochester New York 14623
Department of Chemistry

PERMISSION GRANTED

Title of Thesis: CATALYZED ADDITIONS TO ALKENE DOUBLE BONDS:
(I) FUMARASE-CATALYZED HYDRATION OF ALKENE DOUBLE BONDS
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ACKNOWLEDGMENTS

I would like to personally thank the support of the following people for which this thesis owes its gratitude to:

Dr.Terence C. Morrill, at Rochester Institute of Technology, for his knowledge and guidance throughout my research.

Dr. William Todd and Dr. David Dwyer, at the State University of New York at Brockport, for the use of and training on their NMR spectrometer.

Dr. J. Robert Pipal, at Alfred University, for the use of their MS/GC.

My family and friends for their continuous support and desire to understand my work.

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ABSTRACT

The stereospecific hydration of (*S*)-malate to fumarate, catalyzed by fumarase, was extensively analyzed by NMR. The NMR techniques employed were one dimensional ^{1}H and NOE Difference, and two dimensional ^{1}H-^{1}H COSY. Various potentional substrates were tried for fumarase-promoted hydration with no sucesss. It was concluded that mesaconate is possibly the largest molecule that can fit into the active site of fumarase in the correct orientation for hydration to occur.

Thionyl chloride and appropriately prepared alumina was found to promote the addition of HCl to norbornadiene (**I**), resulting in 71% ($\pm$ 1%) *exo*-5-chloronorbornene (**II**) and 29% 3-chloronortricyclene (**III**) at room temperature, while lower temperatures favor the synthesis of the kinetic product, **III**. Oxalyl chloride and alumina also produces **II** and **III**, but the product composition slowly equilbrates mostly to the thermodynamic product, **III**. Treatment of alumina with deuterium oxide was found to promote the addition of DCl to norbornadiene, when used with thionyl chloride, to give 18% *exo,anti*-5-chlorobicyclo[2.2.1]hept-2-ene-7-d (**VIII**a), 33% exo,exo-6-chlorobicyclo[2.2.1]hept-2-ene-5-d (**VIII**b), 21% 5-chlorotricyclo[2.2.1.$0^{2,6}$]heptane-3-d (**VIII**c), 20% **II**, and 8% **III**. A higher ratio of **VIII**b/**VIII**a for the catalyzed DCl addition than for the uncatalyzed addition[1]

suggests that the 1,2-addition, when using alumina, gives a somwhat higher proportion of *syn*-addition.

PART I

FUMARASE-CATALYZED HYDRATION OF DOUBLE BONDS

INTRODUCTION

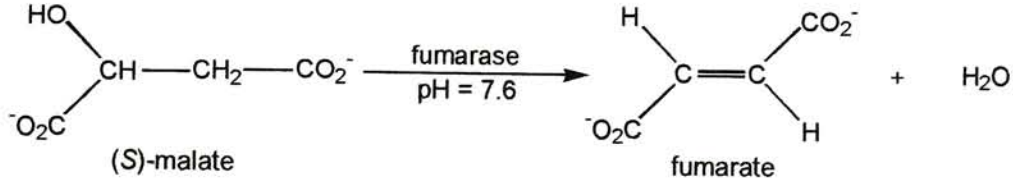
Fumarase is a well known enzyme that catalyzes the reversible hydration of fumarate to (*S*)-malate[2]. Since it is part of the citric acid cycle, it is present in most organisms. The enzyme can be found in the mitochondria of eukaryotes and in the plasma membrane of prokaryotes. There, it plays an important role in the complex process[3] of converting sugars into energy in both aerobic and anaerobic metabolisms.

The simple dehydration and hydration reactions of (*S*)-malate and fumarate, respectively, can be seen in **Scheme I**. Fumarase hydrates fumarate and dehydrates (*S*)-malate stereospecifically,[4] and detailed sawhorse representations and Newman projections are shown in **Scheme II**. However, since the proton added via hydration to fumarate cannot be distinguished from the other methylene proton of (*S*)-malate, it is necessary to use a labeled addendum: D_2O. This can be seen is **Scheme III**.

NMR is a valuable tool for monitoring labeled atoms that have been incorporated in such a fashion. When a ^1H NMR probe is used, structural deuterium atoms will not appear in the spectrum. Because of the commercial availability of isotopes, a chemist can take advantage of this to learn more about the mechanism of a reaction.

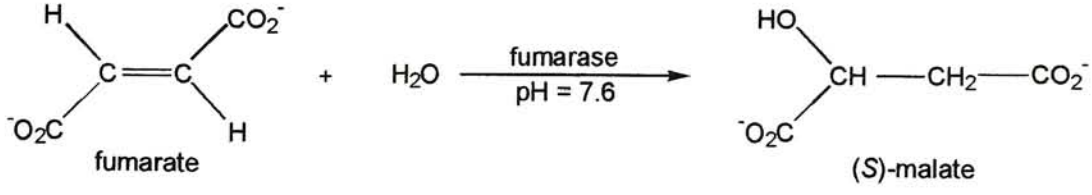
Scheme I

Dehydration:



(*S*)-malate fumarate

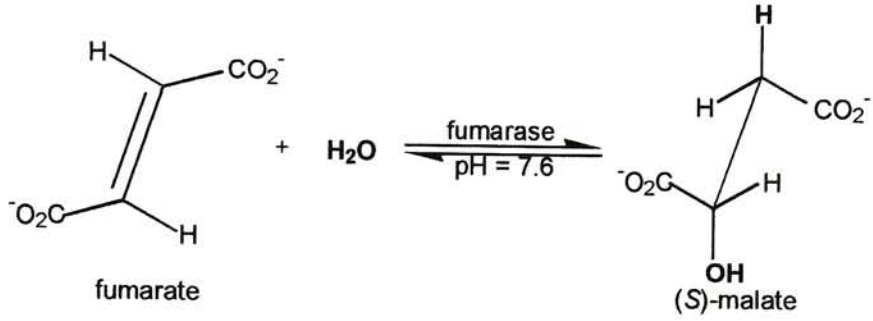
Hydration:



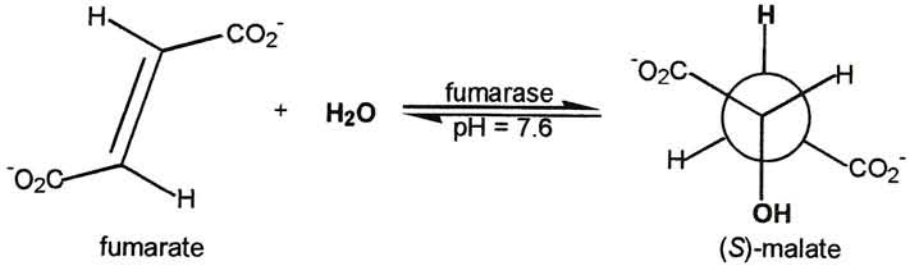
fumarate (*S*)-malate

Scheme II

Sawhorse Representation

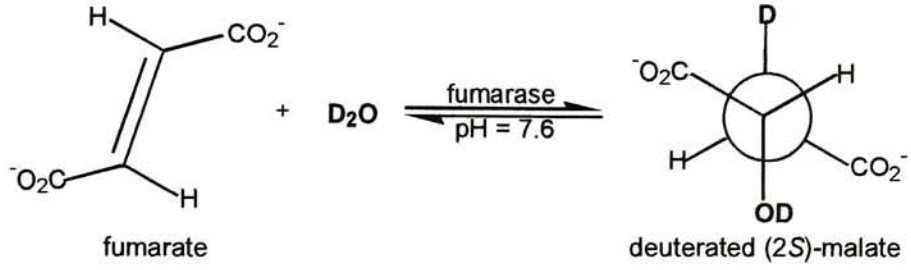


Newman Projection



Scheme III

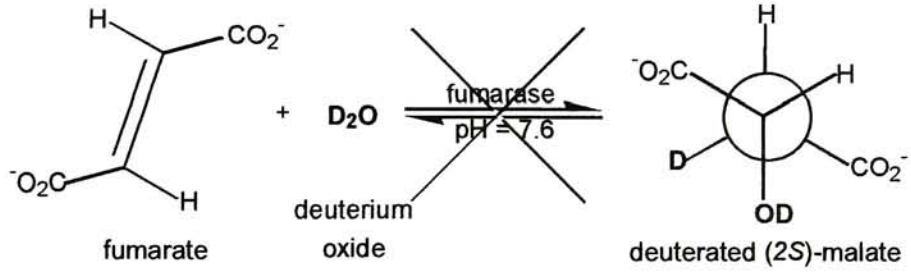
Observed:



fumarate

deuterated (2*S*)-malate

Not seen:

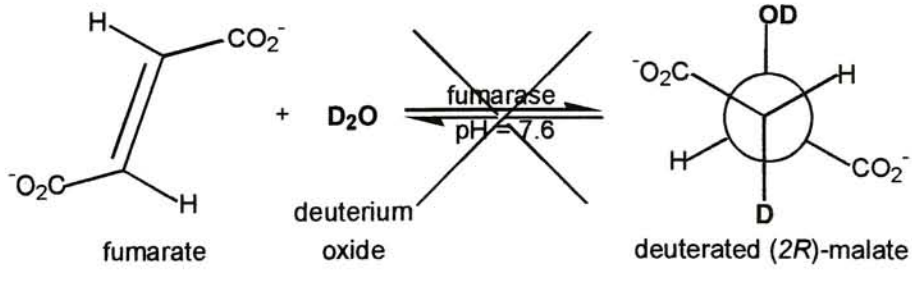


fumarate

deuterium oxide

deuterated (2*S*)-malate

Not seen:



fumarate

deuterium oxide

deuterated (2*R*)-malate

^{1}H NMR has been extensively used to monitor fumarase-catalyzed reactions.[4,5,6,7,8] This has been done by running hydration reactions in a buffered solution of sodium deuteroxide and deuterium oxide. The deuterium and deuteroxyl group add in anti fashion to the alkene double bond of fumarate. Likewise when the reaction is run using a deuterated (*2S*)-malate, only the deuteron or proton anti to the deuteroxyl group is removed (**Scheme III**). Only one product is synthesized out of the four possible stereoisomers of deuterated malate.

To understand why this fumarase-catalyzed reaction is stereospecific, it is necessary to know more about fumarase and the arrangement of its active site.

Fumarase is a tetramer and, for example, in porcine heart fumarase, each subunit consists of 466 amino acids, giving a total of 1864 residues[9]. This type of fumarase is composed of approximately 50% α-helix, and it has neither disulfide bonds nor cofactor requirements. The enzyme possesses four active sites,[10] and if the subunits are separated, they show no catalytic ability.[11] It was only recently that the three dimensional structure has been determined and the location of its active sites of fumarase C from Escherichia coli has been found.[12]

The four subunits, each shown in a separate color, of fumarase C from Escherichia coli can be seen in **Figure I**. Each active site is located at the corners of the enzyme and is formed by the intersection of three of the four subunits (**Figure II**). Lys 324A (shown in blue), and possibly another residue on the opposite side of the pocket,[5] are positively charged binding sites that anchor onto

Figure I : [12] The 3 dimensional representation of fumarase C from Escherichia coli

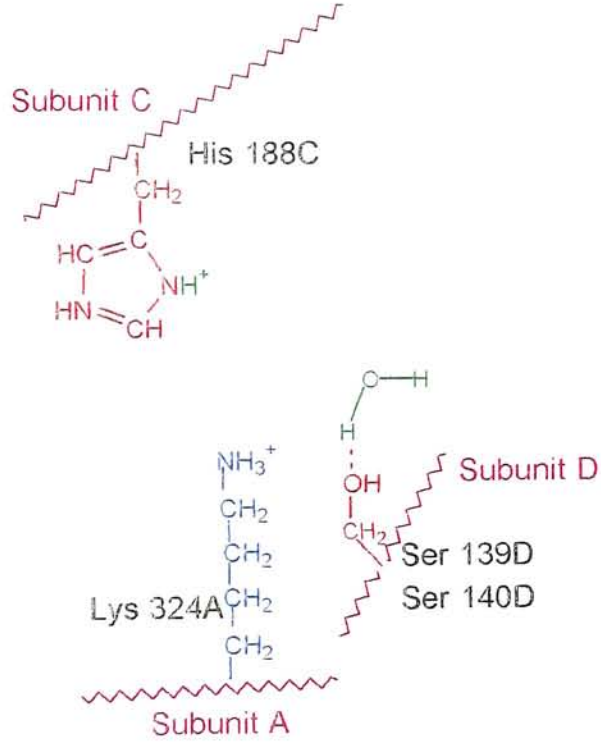


Figure II : The active site of fumarase C from Escherichia coli

Hydration:

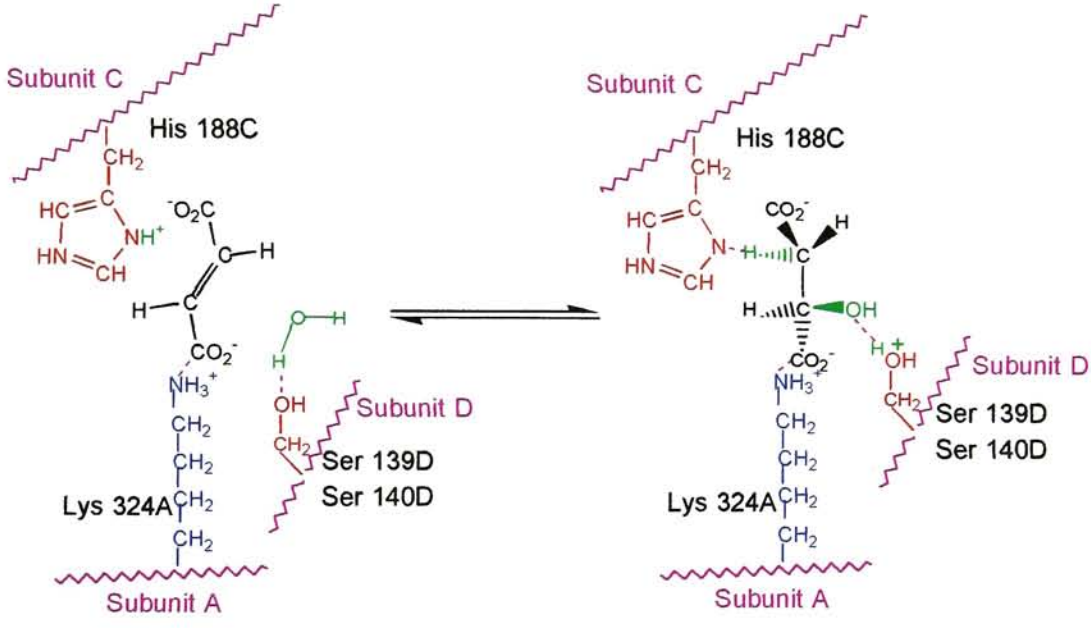


Figure III : The hydration of (*S*)-malate to fumarate in the active site

the negatively charged carboxylate groups of the substrate (**Figure III**). It also helps to position the substrate into the correct orientation for catalysis. Next, either (or both) Ser 139D or Ser 140D (both shown in red) add a hydroxyl group to one side of the double bond of the substrate, while His188C (also shown in red) protonates the other side. The result is a compound that is hydrated stereospecifically. Addition of D_2O proceeds in a similar fashion (**Figure IV**).

Fumarase has been shown to catalyze the hydration of substrates other than fumarate.[5,11,13,14,15] Many of these substrates are similar in structure to fumarate. These substrates posses a double bond with two anti carboxylate groups (**Scheme IV**). Substitution of X in **Scheme IV** gives rise to the products presented in **Scheme V**. Fluorofumarate gives (*R*)-2-fluoro-2-hydroxysuccinate, instead of (*2R,3S*)-3-fluoro-2-hydrosuccinate (**Scheme VI**). One substrate that is hydrated by fumarase is acetylene dicarboxylate. It is interesting to note that since it has a triple bond instead of a double bond, the carboxylate groups are not anti. The substrate is hydrated in a similar fashion as previous described to give an enol intermediate. It undergoes rearrangement to oxaloacetate (**Scheme VII**) formed by the tautomerization of the enol intermediate.

Deuterated Hydration:

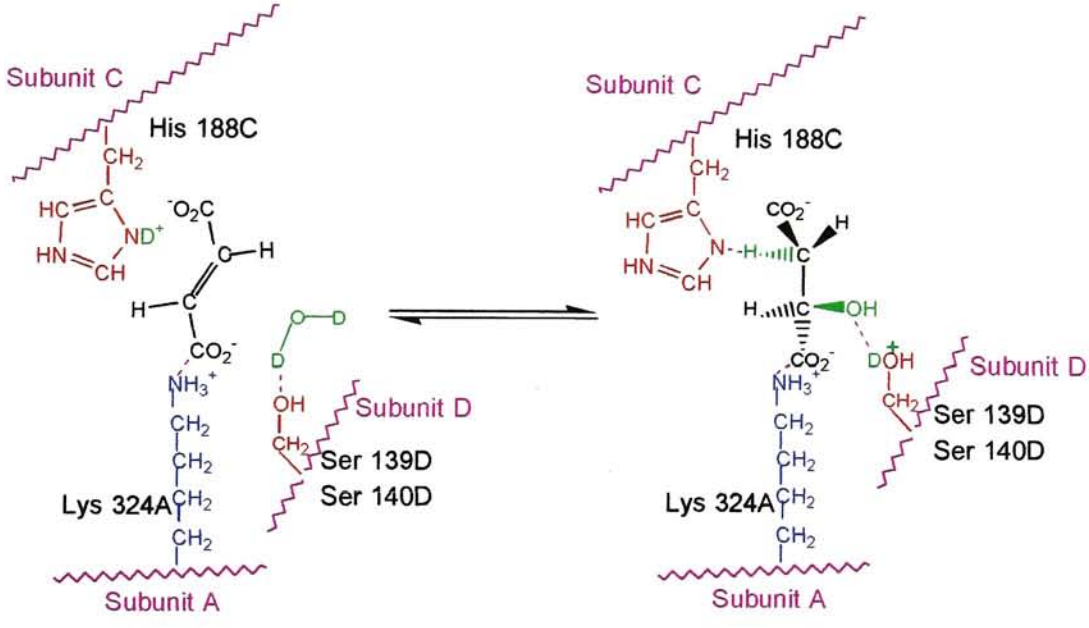
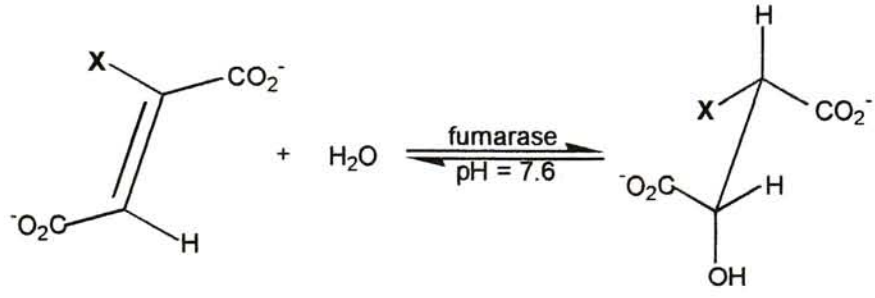


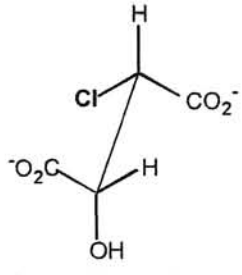
Figure IV : The addition of D_2O (*S*)-malate to fumarate in the active site

Scheme IV

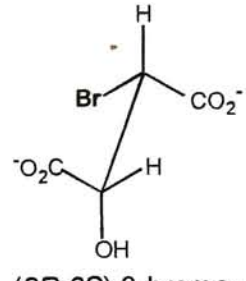


X = Cl, Br, I, CH_3, OH, NH_2

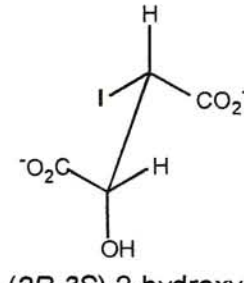
Scheme V



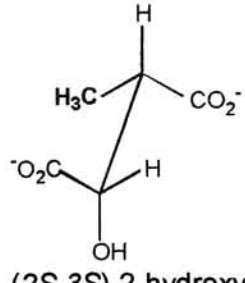
(*2R,3S*)-3-chloro-2-hydroxysuccinate



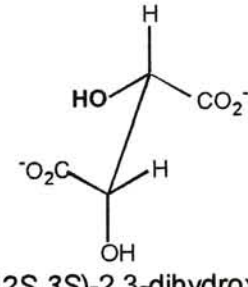
(*2R,3S*)-3-bromo-2-hydroxysuccinate



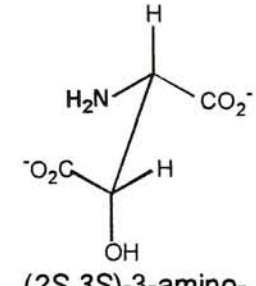
(*2R,3S*)-2-hydroxy-3-iodosuccinate



(*2S,3S*)-2-hydroxy-3-methylsuccinate



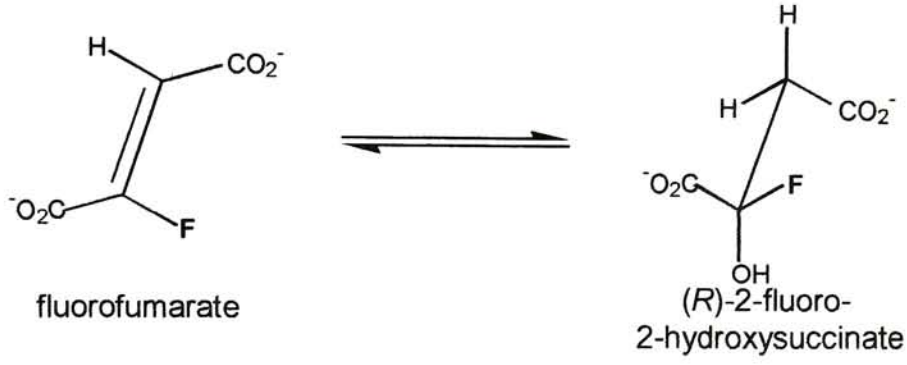
(*2S,3S*)-2,3-dihydroxy-succinate



(*2S,3S*)-3-amino-2-hydroxysuccinate

Scheme VI

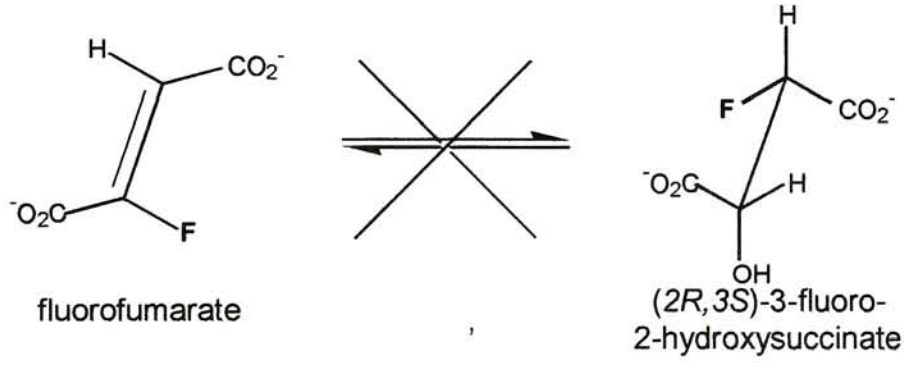
Observed:



fluorofumarate

(*R*)-2-fluoro-
2-hydroxysuccinate

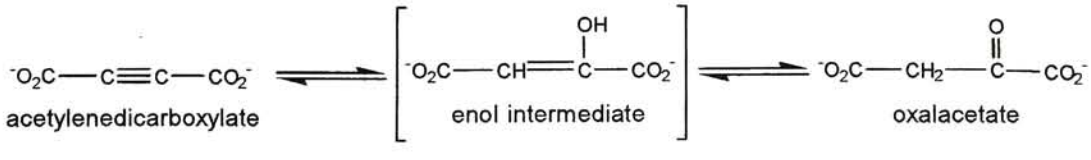
Not seen:



fluorofumarate

(*2R,3S*)-3-fluoro-
2-hydroxysuccinate

Scheme VII



EXPERIMENTAL

General procedures. All reactions were done at room temperature and in disposable glassware and NMR tubes. All spectra were obtained on a 300 Mhz Bruker NMR in a solution of deuterium oxide buffered to pH = 7.5 with NaOD. Fumarase-ammonium sulfate suspension (cat# F 1757), fumaric acid (cat# F 2752), and (*L*)-malic acid monosodium salt (cat# M 9138) were from Sigma Chemical Company, St. Louis, MO. All other chemicals were from Aldrich Chemical Company, Inc., Milwaukee, WI.

Fumarate and (*S*)-malate reactions. (Reactions were followed as previously described,[8] except the solutions were buffered to pH = 7.5.) Either (*L*)-malic acid monosodium salt or fumaric acid was diluted with deuterium oxide (cat# 15,188-2) to 0.2 M, and buffered to pH = 7.5 with 0.13 M disodium hydrogen phosphate (cat# 21,988-6) and sodium deuteroxide (cat# 17,678-8). The fumarase-ammonium sulfate suspension was diluted 1:20 with deuterium oxide. A charge of 0.2 ml of the fumarase solution and 0.5 ml of the substrate solution (either (*S*)-malate or fumarate) was placed in a NMR tube, shaken, and allowed to react for 72 hours.

Mesaconate and potential substrate reactions (method 1). The following were each substituted for the fumarate substrate in the **fumarate and (*S*)-malate**

reactions procedure: mesaconic acid (cat# 13,104-0), trans-aconitic acid (cat# 12,275-0), trans-glutaconate (cat# 36,953-5), trans,trans-muconic acid (cat# M9,000-3), and trans-β-hydromuconic acid (cat# H1,785-6). Each compound showed no detectable ability to add D_2O when analyzed by NMR, thus the procedure mesaconate and potential substrate reactions (method 2) was implemented.

Mesaconate and potential substrate reactions (method 2). Mesaconate was reacted with fumarase and water as previously described,[5] except 5 ml of the fumarase-ammonium sulfate suspension was used, and the reaction was run for 14 days. Mesaconate was found to undergo fumarase-promoted hydration. However when trans-aconitate, trans-glutaconate, trans,trans-muconate, and trans-β-hydromuconate were each substituted for mesaconate as described above, no fumarase-promoted hydration was found for any of the reactions when analyzed by NMR.

Fumarate-fumarase inhibition reactions. Mesaconate, trans-aconitate, trans-glutaconate, trans,trans-muconate, and trans-β-hydromuconate were each tested for its ablility to inhibit the reaction of fumarate to (*S*)-malate. A solution of 0.2 M fumarate and 0.2 M of each inhibitor was prepared and reacted as described in

fumarate and (*S*)-malate reactions. For each of reaction, fumarate required a longer period of time to reach equilibration than without the added inhibitor.

RESULTS AND DISCUSSION

Using high field NMR, the two protons β to the hydroxyl group in (*S*)-malate can be easily seen to be nonequivalent diastereotopic. Using a 300 MHz ^{1}H NMR instrument, the three proton signals of (*S*)-malate are found to be first order; thus, it is label an AMX system. At this resolution, the stereochemistry of the hydration of the fumarate catalyzed by fumarase can easily be studied.

Since fumarate possess two equivalent olefinic protons, a ^{1}H NMR spectrum shows only one signal (δ 6.56, **Figure V**), and also the 2D COSY spectrum shows no coupling nor interaction with these olefinic protons (δ 6.56, **Figure VI**). The presence of the H_2O or HOD impurity in the heavy water solvent is revealed by a peak of significant size at δ 4.87.

The spectrum for S-malate, however, is found to be quite detailed (**Figure VII**). It has one signal for each of the three protons. These will be labeled H_A, H_M, and H_X for the signals at δ 2.42, δ 2.73, and δ 4.35, respectively. A 2D HETCOR spectrum reveals that H_A and H_M are two protons on the same methylene carbon β to the hydroxyl group, and H_X is the proton that is α to the hydroxyl group. Protons H_A, H_M, and H_X are each doublet of doublets, as shown in the expanded signals in **Figure VIII**. Analyzing the 2D COSY spectrum (**Figure IX**) reveals the fact that each proton is coupling with the other two, and three different J values are observed (**Figure X**). Using the ^{1}H NMR splittings of S-malate, the values for J_{AM}, J_{AX},

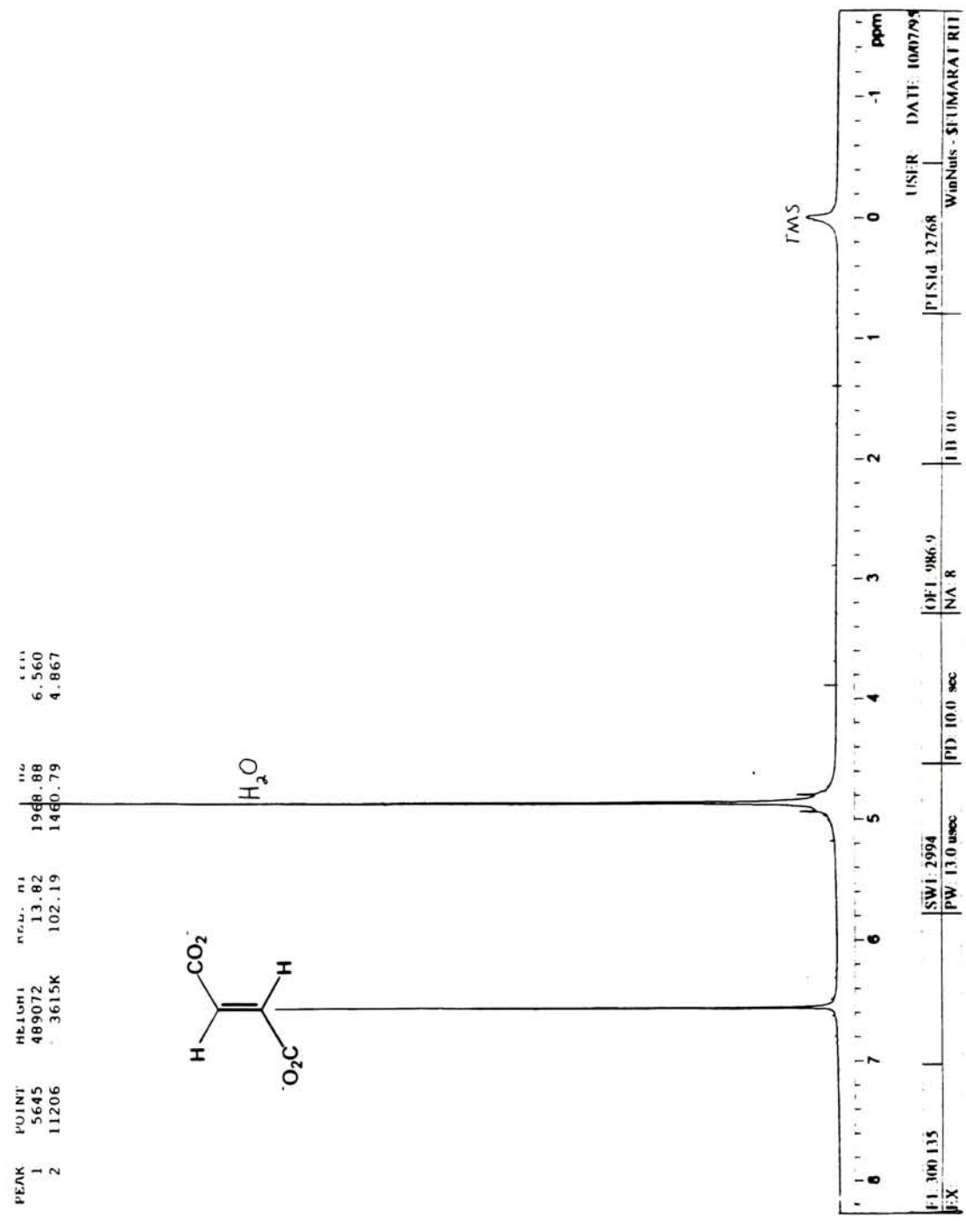


Figure V : The ^1H NMR spectrum of fumarate in D_2O, adjusted to pH = 7.5 with NaOD

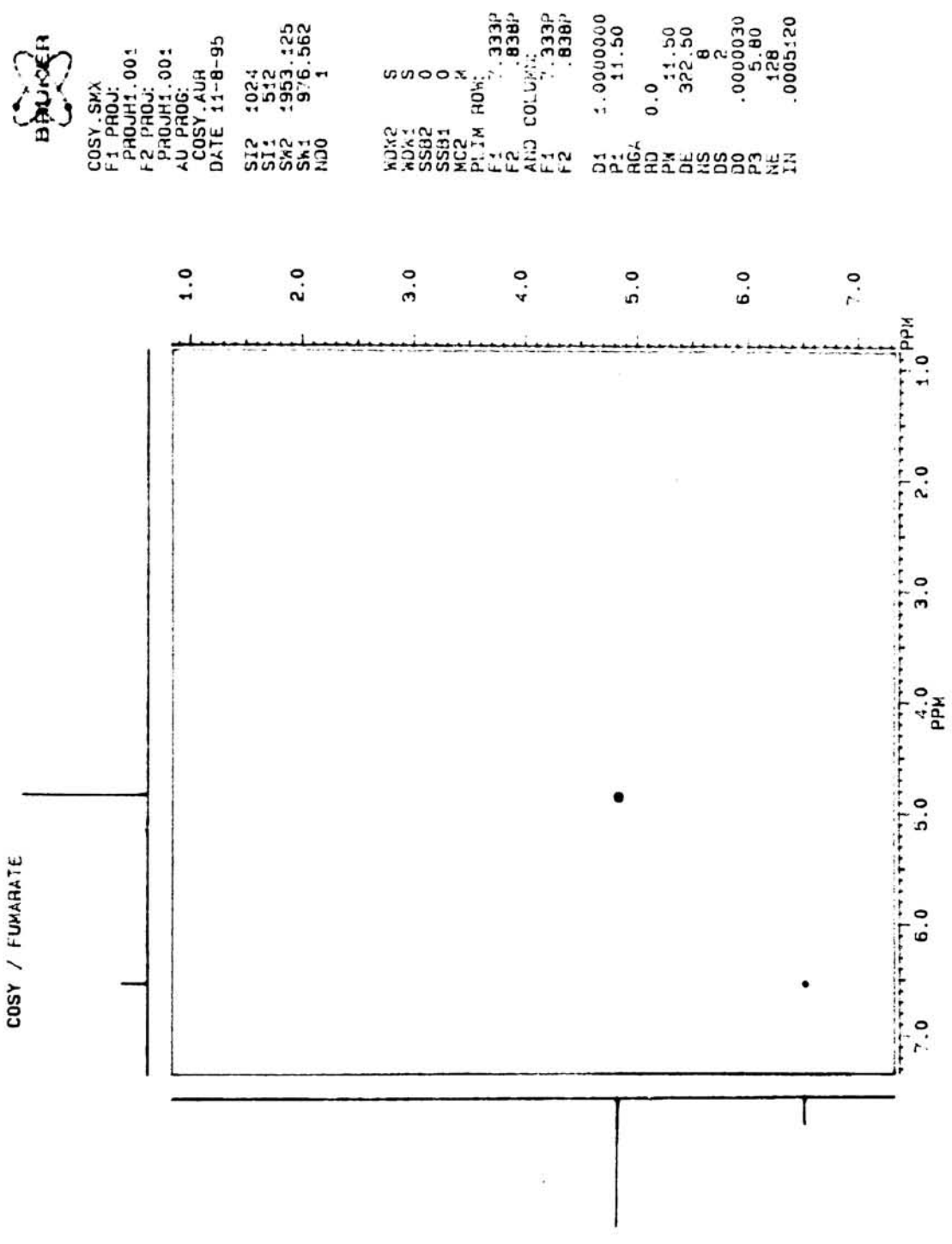


Figure VI : The 2D ^{1}H-^{1}H COSY of fumarate in D_2O, adjusted to pH = 7.5 with NaOD

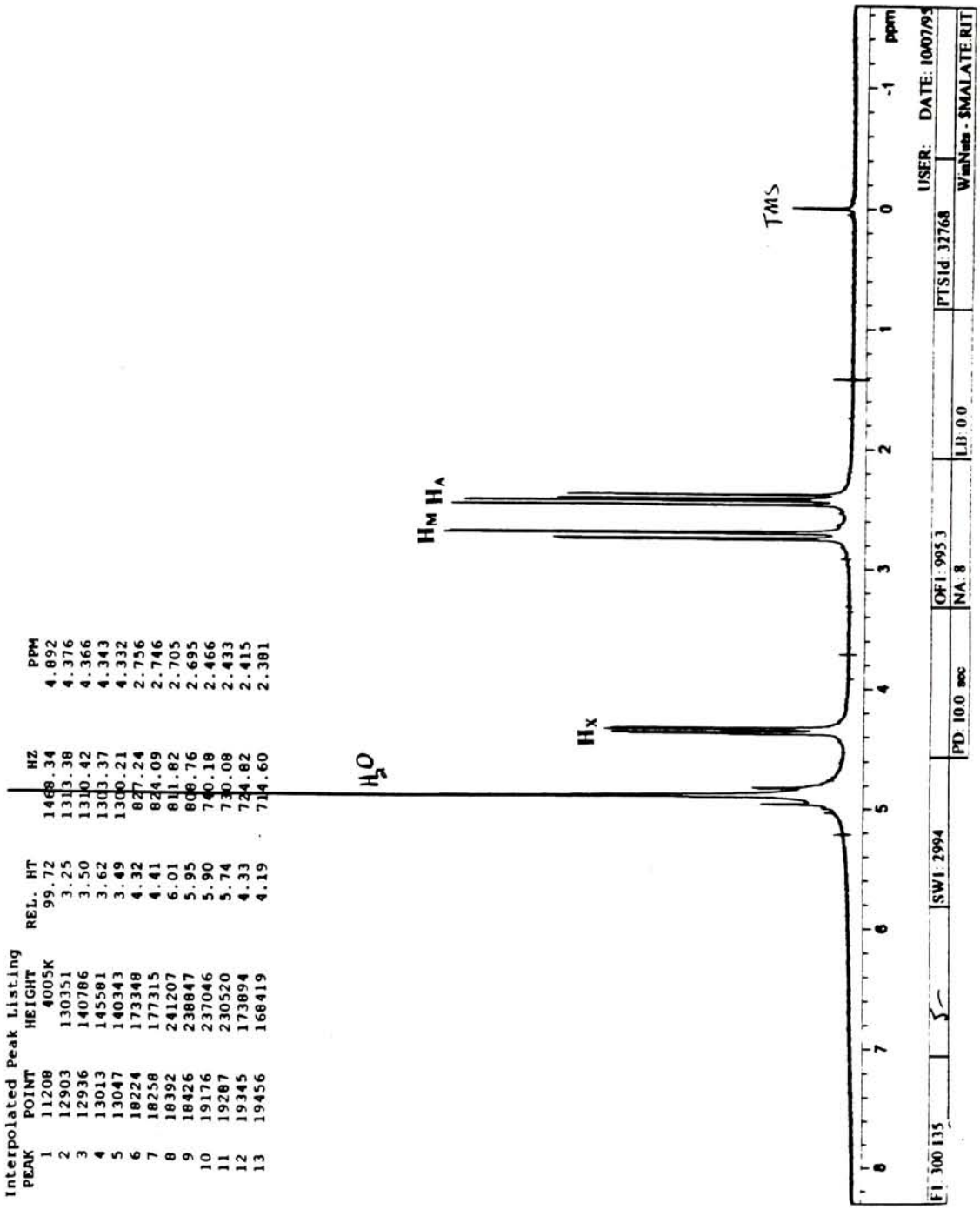


Figure VII : The ^{1}H NMR spectrum of (S)-malate in D_2O, adjusted to pH = 7.5 with NaOD

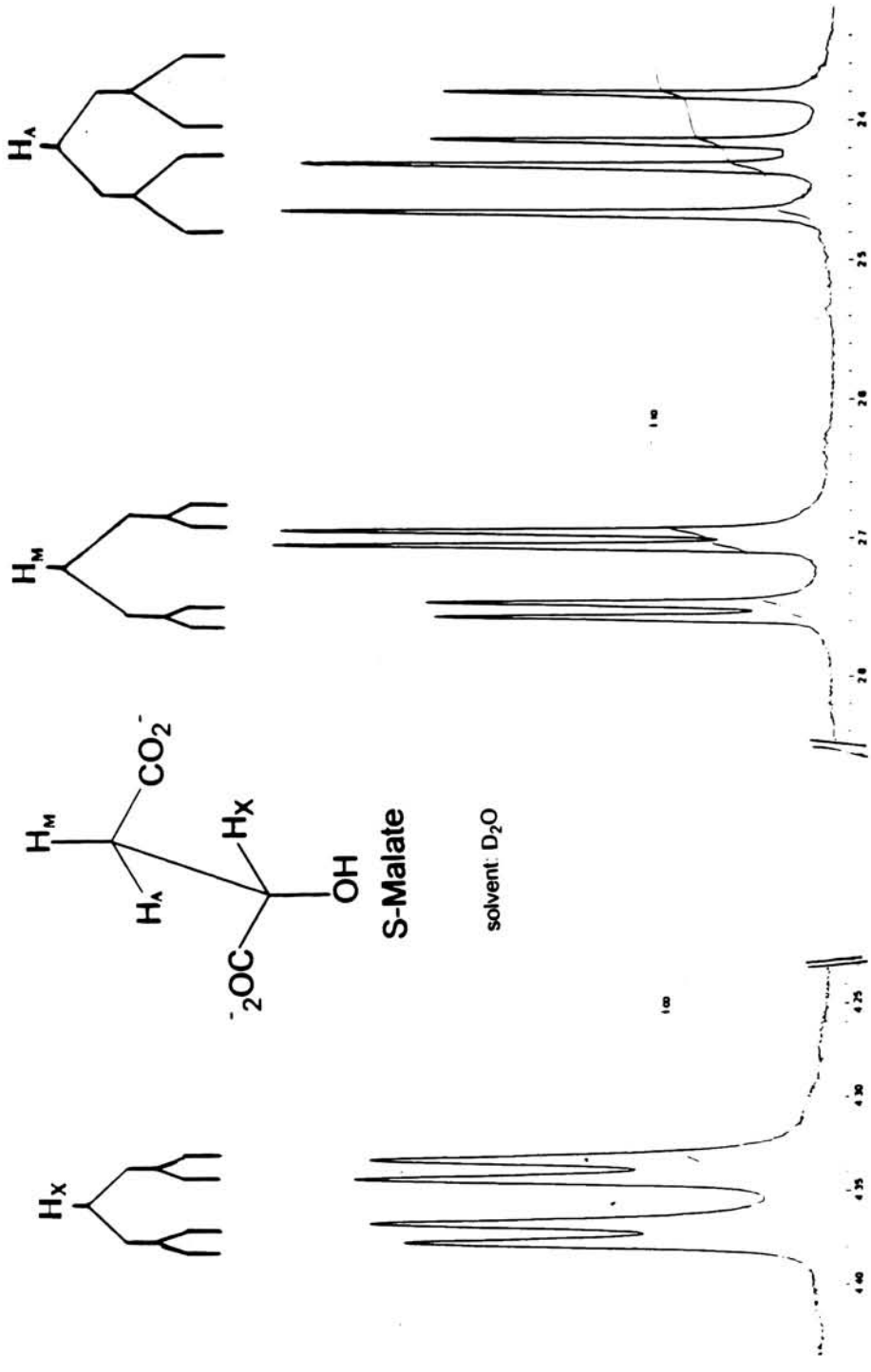


Figure VIII : The labeled ^{1}H-NMR of (S)-malate in D_2O, adjusted to pH = 7.5 with NaOD

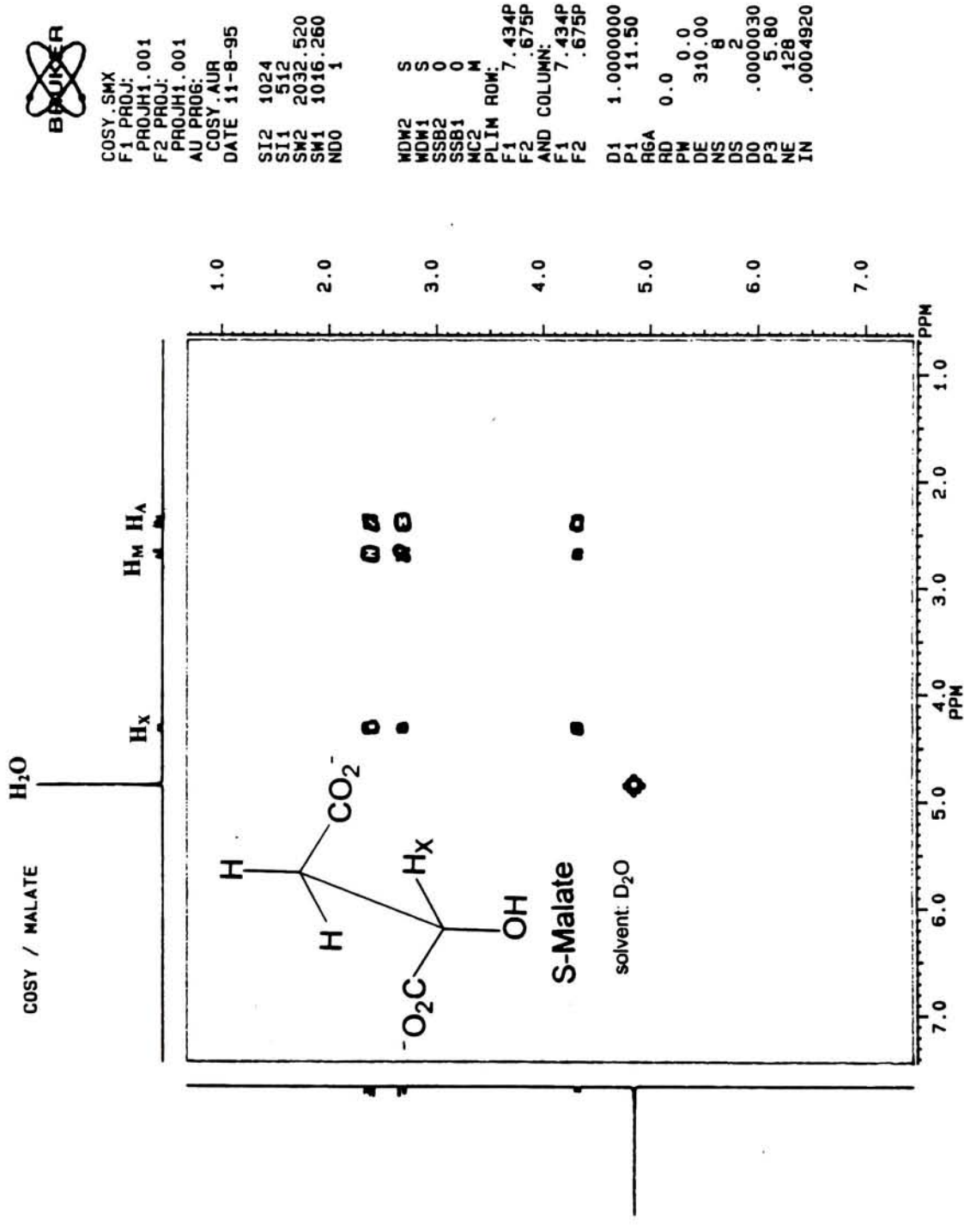


Figure IX : The 2D COSY of (S)-malate in D_2O, adjusted to pH = 7.5 with NaOD

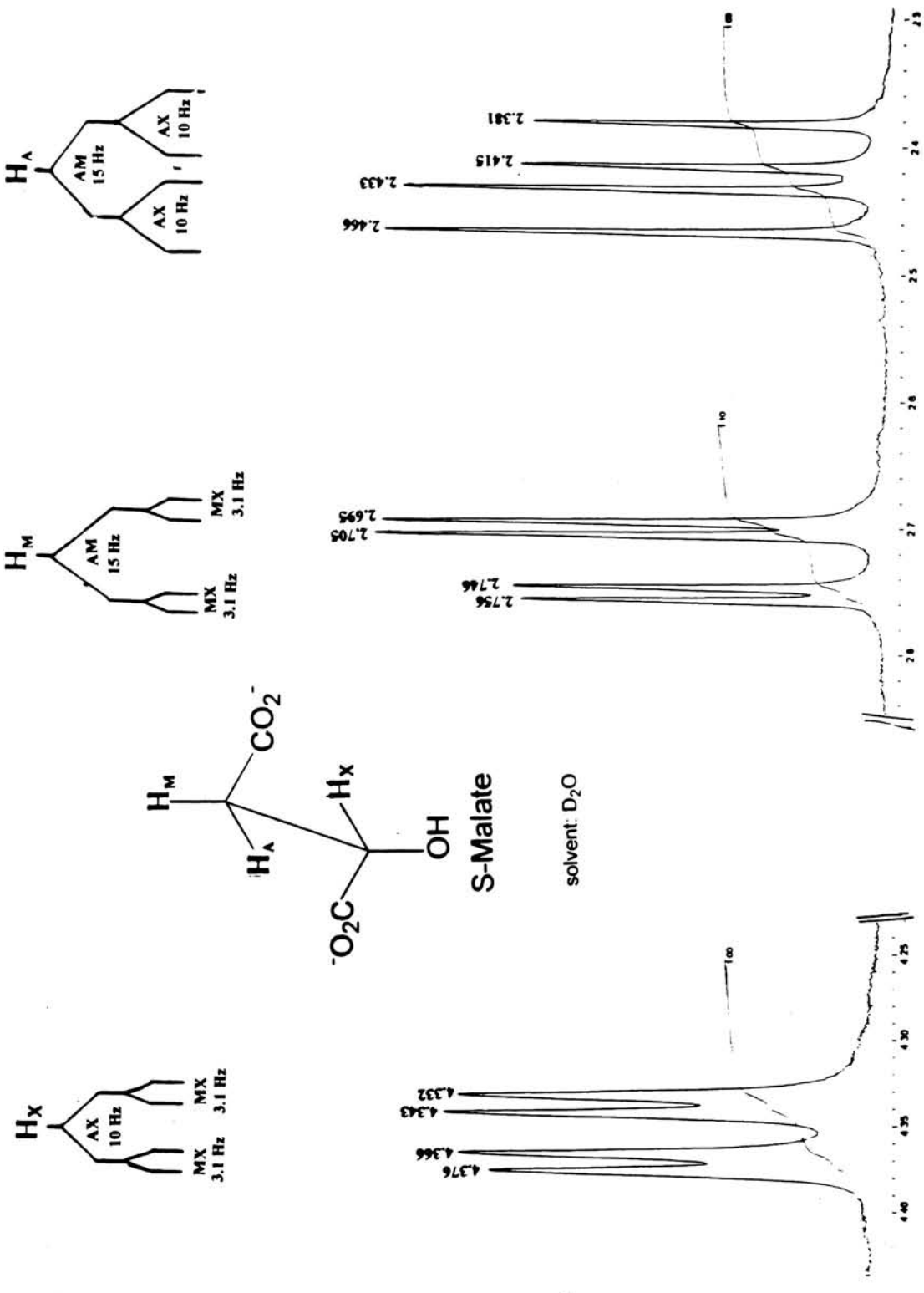


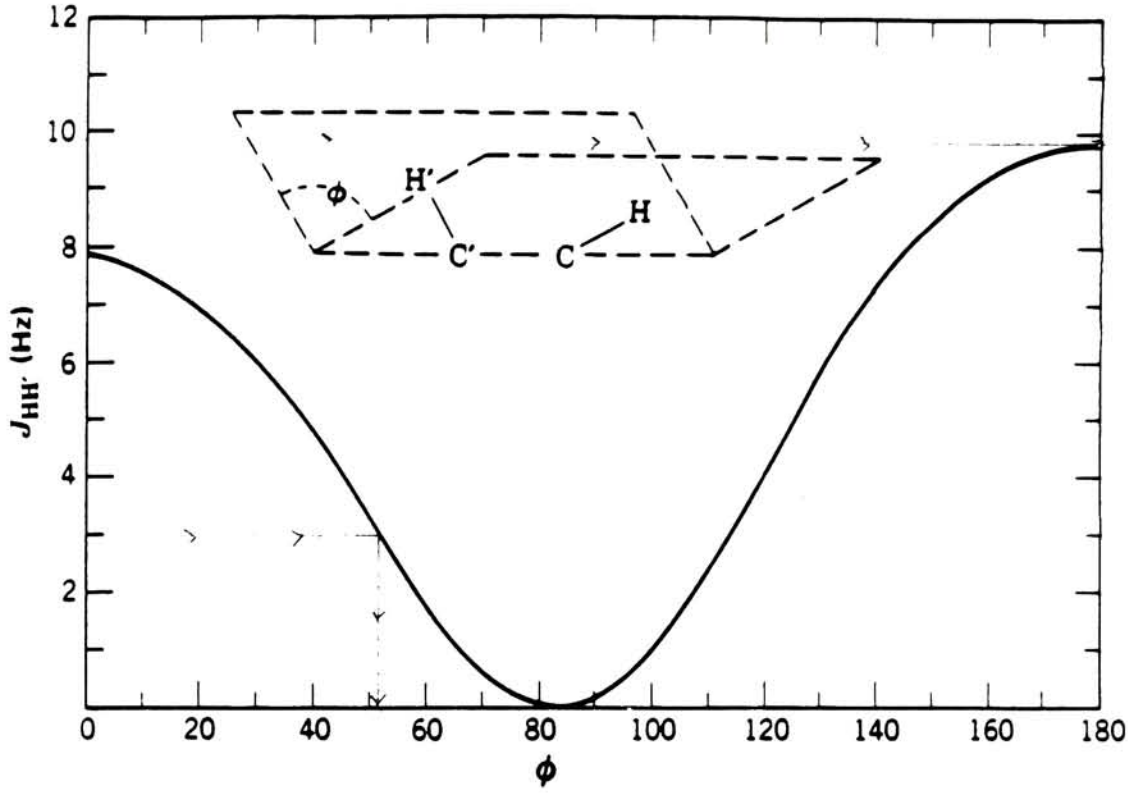
Figure X : Coupling constants of the labeled ^{1}H NMR of (S)-malate in D_2O, adjusted to pH = 7.5 with NaOD

and J_{MX} are assigned as, respectively 15 Hz, 10 Hz, and 3.1 Hz, based on the discussion below.

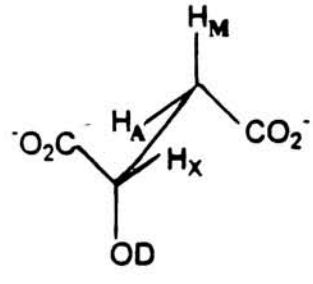
Proton H_X is responsible for the farthest downfield signal (δ 4.35), because of the added desheilding effect of the hydroxyl group. Protons H_A and H_M can be assigned by two methods. One is by using a vicinal Karplus correlation, and the other is done by using 1D ^{1}H-NMR NOE difference spectroscopy.

The relationship between dihedral angle and J coupling values is displayed in the vicinal Karplus correlation graph (**Figure XI**). Using the coupling constant for J_{AX} (3.1 Hz) on this graph, a dihedral angle (ϕ) of about 50° is suggested; this is a close to the angle of 60° expected for H_M and H_X assuming that the Newman projection in **Figure XI** is the predominate structure. Similarly, a coupling constant of 10 Hz for J_{AX}, suggests a dihedral angle of 180°; this matches the angle of the H_A/H_X geometry in the same projection.

The second way that H_A and H_X can be assigned is by taking advantage of proton-proton, through-space distances as measured by NOE Difference methods. The nuclear Overhauser effect will result in the enhancement of the signals of protons separated by a distance of 4 Å or less from the proton that has been irradiated. Since enhancement of peaks is sometimes difficult to see, it is beneficial to subtract out an "unirradiated" spectrum from the irradiated spectrum. By doing this, unenhanced signals (due to protons with no close neighbors) give rise to virtually nonexistent peaks. Enhanced signals, however, give rise to substantial peaks and are thus easily distinguished from the others. Looking at a spectrum of (*S*)-malate that has been



The vicinal Karplus correlation. Relationship between dihedral angle (ϕ) and coupling constant for vicinal protons.



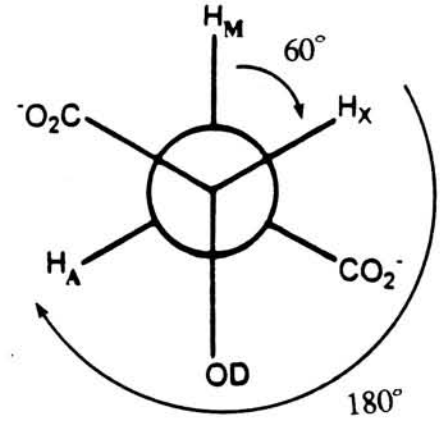


Figure XI : Vicinal Karplus correlation chart[16]

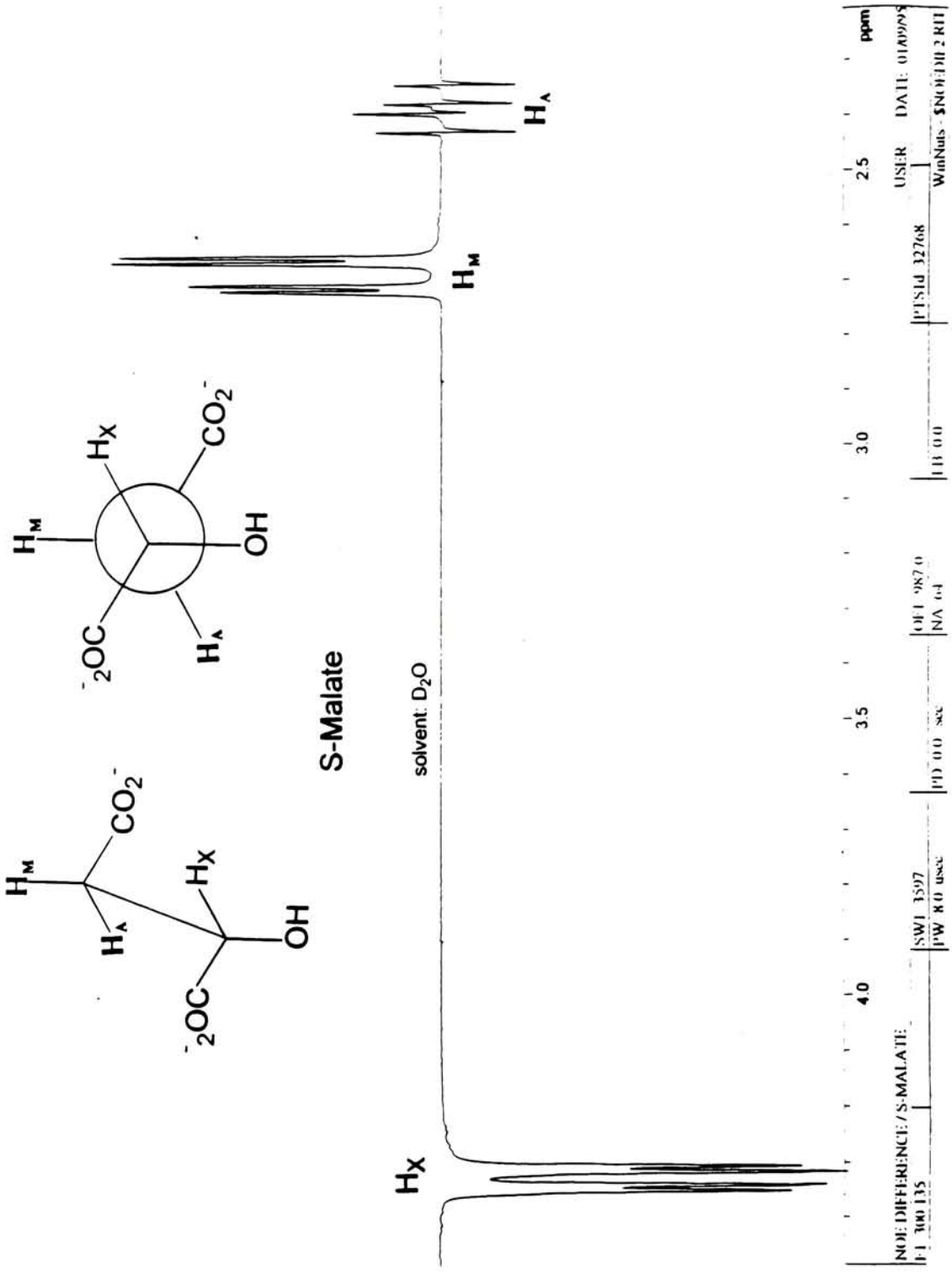


Figure XII : The labeled ^{1}H-NMR NOE Difference (irradiated at δ 4.35) of (S)-malate in D_2O, adjusted to pH = 7.5 with NaOD

irradiated at H_X (δ 4.35, **Figure XII**), it can be seen that H_M is enhanced and H_A is not. So, we can conclude that H_M is the one that is in closer proximity to H_X, which is consistent with the 60° dihedral angle. Since H_A shows no enhancement, it can be concluded that H_X and H_A are not close. A spectrum that has been irradiated at H_A (**Figure XIII**), suggests that H_A is close enough to H_M to cause an enhancement. It can also be concluded that the two protons H_A and H_X are far apart, since H_X was not enhanced (consistent with a dihedral angle of 180°).

When either fumarate or S-malate are allowed to react with deuterium oxide (adjusted to a pH = 7.6 with sodium deuteroxide) and fumarase until equilibrium (72 hours) is reached, they result in a similar spectrum (shown in **Figure XIV**). This spectrum shows that fumarate and deuterated S-malate are present. More to the point, the H_A and H_X signals of S-malate are present, but H_M (δ 2.73) is absent. H_A and H_X are no longer doublet of doublets; they are both doublets. Also, the 2D COSY spectrum (**Figure XV**) shows that only H_A and H_X are coupled. These observations can be explained by the position of the deuterium atom. As described earlier, we expect that fumarate places a deuterium anti to the OD group, the H_M signal disappears leaving only H_A and H_X (**Figure XVI**). The splitting patterns of H_A and H_X reveal a coupling constant of 10 Hz (J_{AX}). This is in agreement with expectations, described above, based on vicinal coupling. It is also consistent with the loss of any coupling from H_M, since it has been replaced by D which has only negligibly couples to H_A and H_X. Thus fumarase hydrates fumarate stereospecifically,

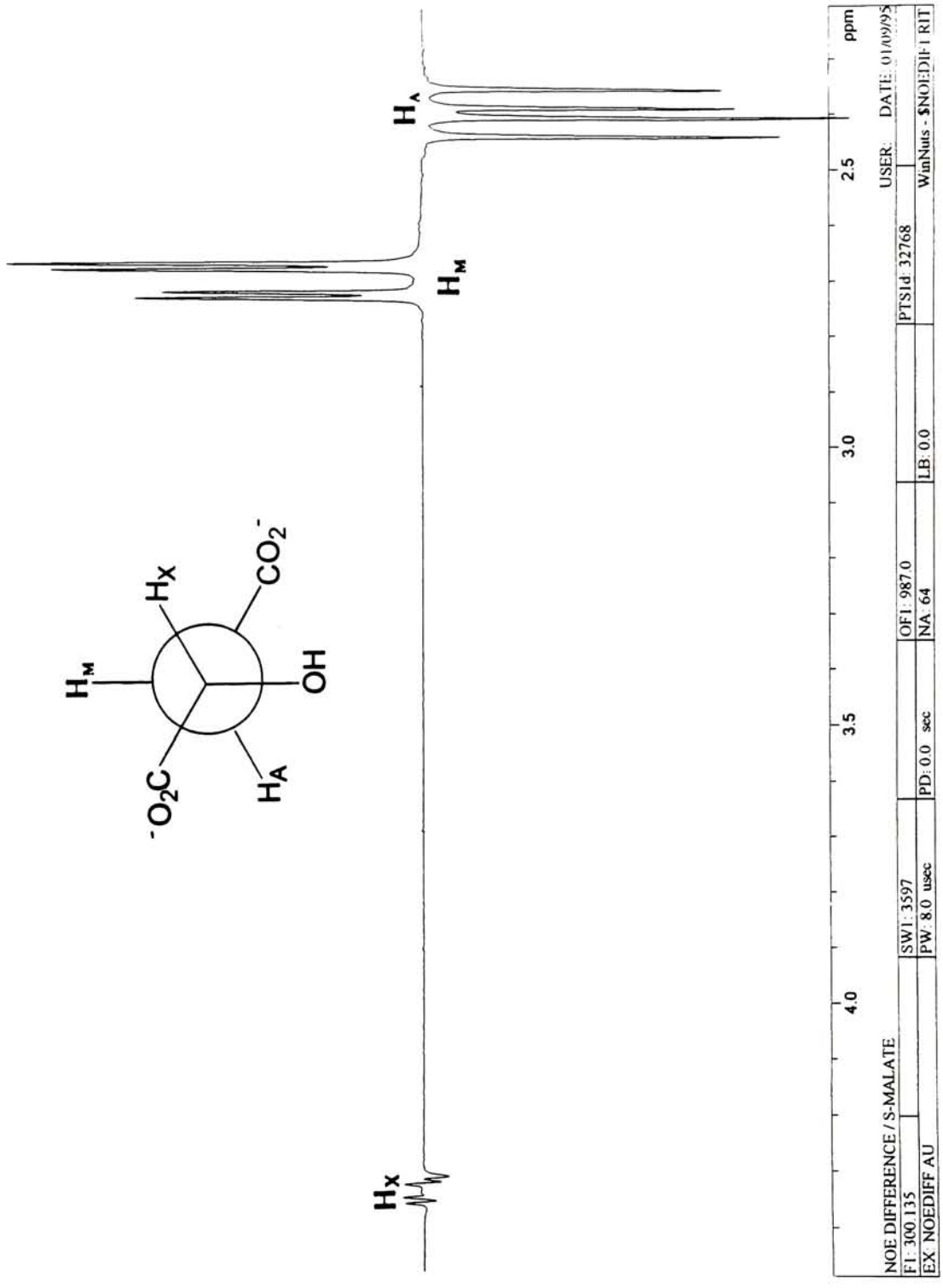


Figure XIII : The labeled ^{1}H-NMR NOE Difference (irradiated at δ 2.42) of (S)-malate in D_2O, adjusted to pH = 7.5 with NaOD

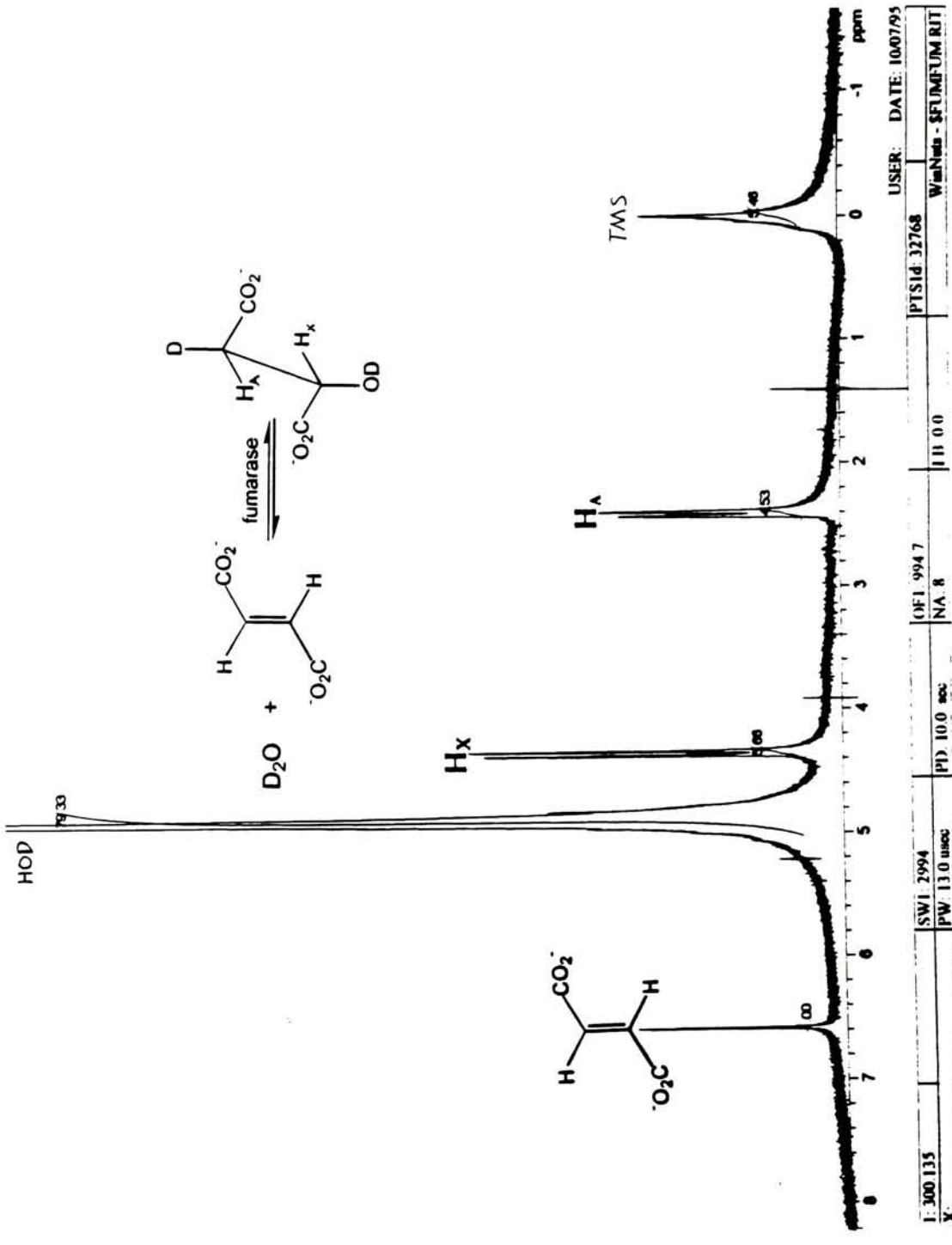


Figure XIV : The labeled ^{1}H-NMR of (S)-malate and fumarase in D_2O, adjusted to pH = 7.5 with NaOD after equilibration (72 hours)

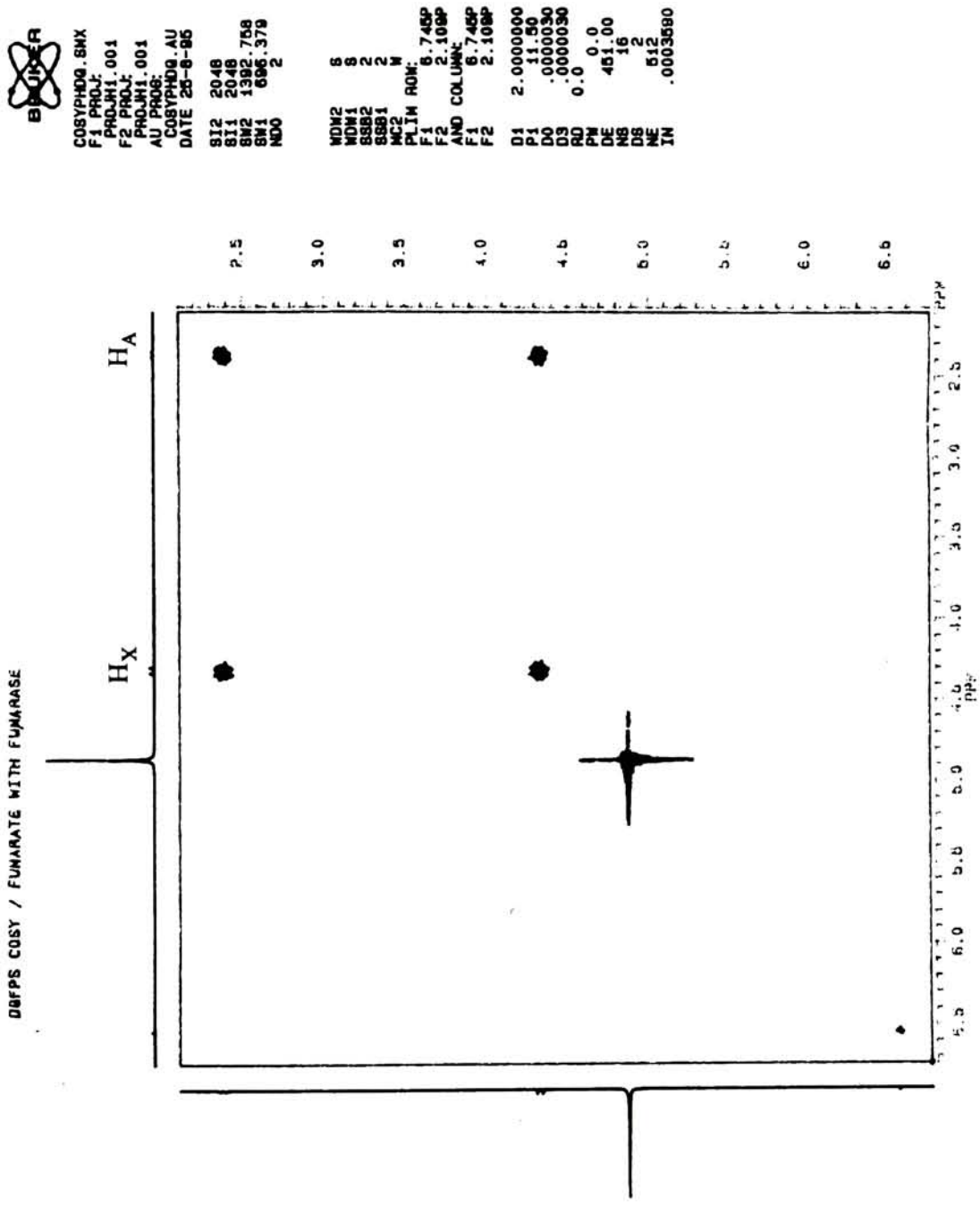


Figure XV : The 2D COSY of (S)-malate and fumarase in D_2O, adjusted to pH = 7.5 with NaOD after equilibration (72 hours)

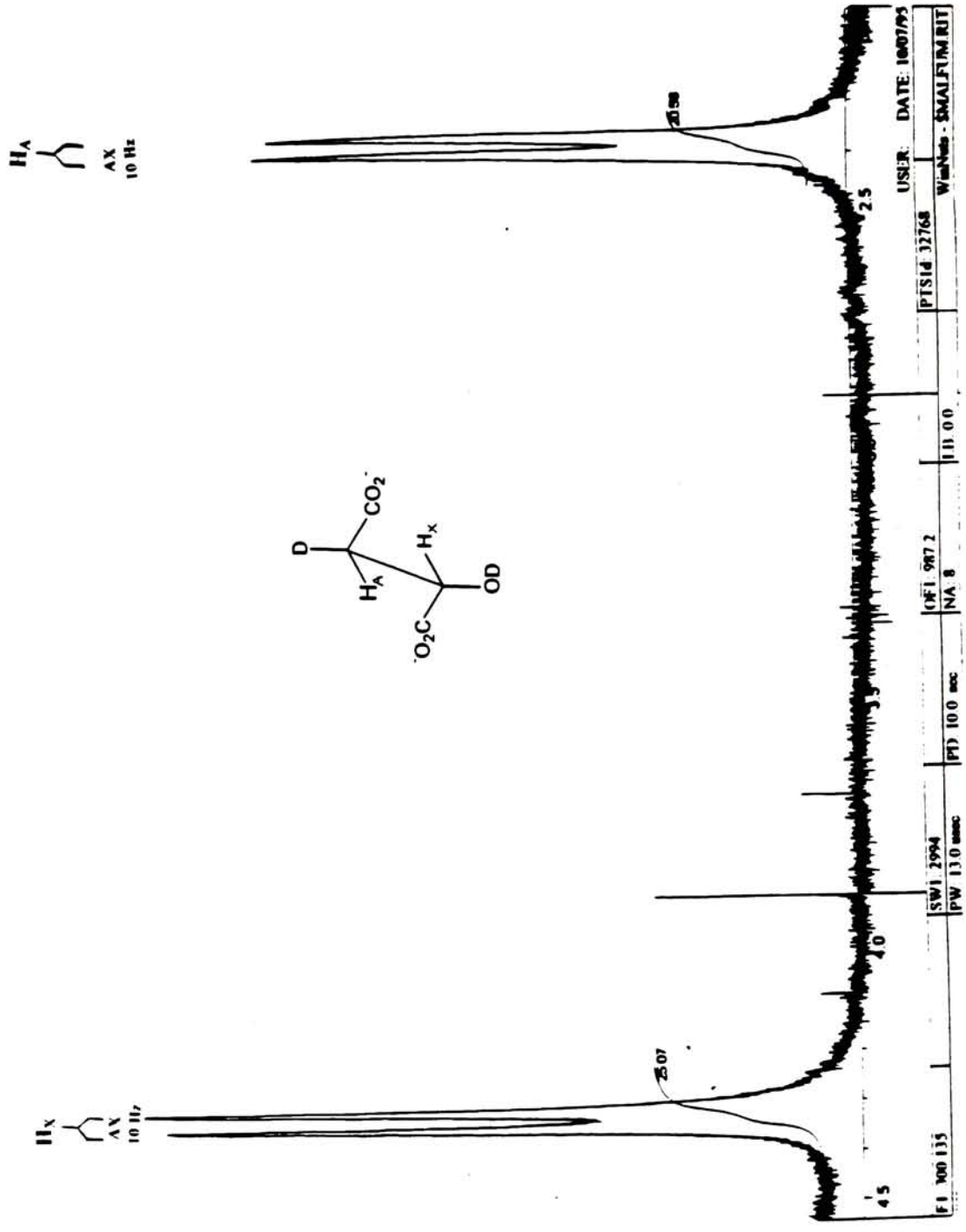


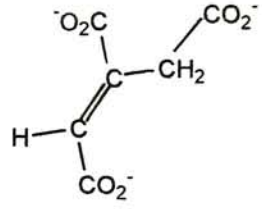
Figure XVI : Close-up of deuterated (S)-malate peaks of the labeled ^1H NMR of (S)-malate and fumarase in D_2O, adjusted to pH = 7.5 with NaOD after equilibration

as described above.

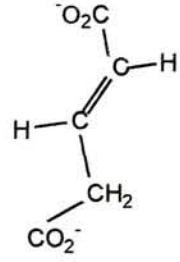
Since fumarase had been found to hydrate the double bonds of molecules that are similar in structure to (*S*)-malate[5], investigation of which substrates could be synthetically transformed was carried out. This information also might be beneficial in learning more about the active site of the enzyme.

Several potential substrates were selected to be tested for the catalyzed-hydration by fumarase. The method of selection was as follows: the potential substrate should have 1) two carboxylate groups, 2) a double bond between the two carboxylate groups, 3) the carboxylate groups should be on opposite sides of the double bond, 4) it should have a relatively low molecular weight, 5) and it should be commercially available.

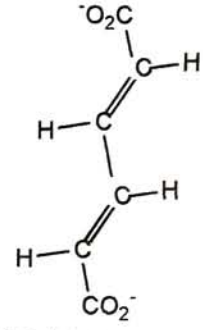
The potential substrates that were selected for study included: trans-aconitate, trans-glutaconate, trans-β-hydromucconate, and trans,trans-muconate (**Figure XVII**). Mesaconate, which had been previously reported to work,[5] was allowed to react with deuterium oxide and fumarase, buffered at pH = 7.5. This buffer was prepared similarly to that used in the reactions of fumarate and S-malate. Hydration of each of the substrates was not detected by ^{1}H-NMR nor ^{13}C-NMR. Taking into account that the reaction would likely proceed at a slower rate than fumarate, the concentration of fumarase was increased 10,000-fold. This then afforded a very small amount of hydrated product, as per weak NMR signals.



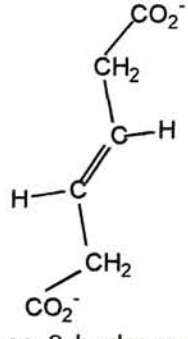
trans-aconitate



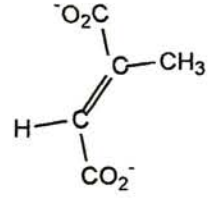
trans-glutaconate



trans,trans-muconate



trans-β-hydromuconate



mesaconate

Figure XVII : Mesaconate and other substrates proposed for fumarase-promoted hydration

Duplicate reactions were attempted, substituting each of the potential substrates for mesaconate. After no product was found, the duration of the reaction for each of potential substrates (**Figure XVII**) was increased from 3 days to 14 days. Again, no detectable hydration was observed. However, these compounds were found to act as a competitive inhibitors when added to the fumarate-fumarase reaction. This result is understandable, since most compounds with a carboxylate group would compete for the positively charged binding group (Lys 324, in fumarase C from Escherichia coli). As a result the inhibitor would bind to the active site, diminishing the number of active sites available for the fumarate substrate to bind.

Fumarase-promoted hydration is only synthetically viable for synthesizing (*S*)-malate, (*2R,3S*)-3-chloro-2-hydroxysuccinate, and (*S*)-3-Fluoro-oxalacetate.[15] The slow reaction rates and high cost of fumarase prohibit it from being useful in synthesizing other compounds. In addition, fumarase will only accept a small number of substrates.

PART II

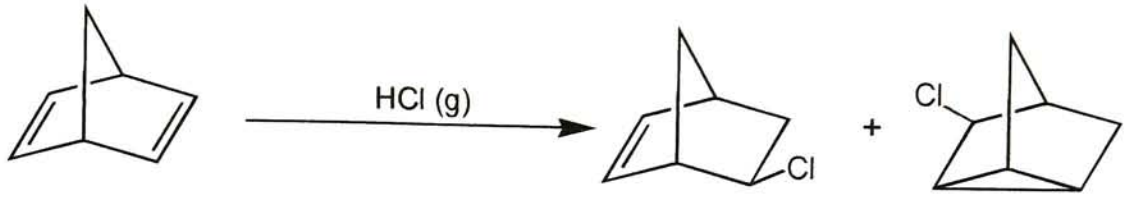
ALUMINA-CATALYZED HYDROCHLORINATION OF ALKENE DOUBLE BONDS

INTRODUCTION

It has been found that norbornadiene (**I**, bicyclo[2.2.1]heptadiene) undergoes hydrochlorination when hydrogen chloride gas is allowed to bubble through a solution of norbornadiene.[1,17] This results in the formation of two isomers, exo-5-chloronorbornene (**II**) and 3-chloronortricyclene (**III**), as seen in **Scheme VIII**. This reaction gives mainly the norbornenyl adduct, **II**. Likewise, hydrobromination of norbornadiene (**I**) gives exo-5-bromonorbornene (**IV**) and 3-bromonortricyclene (**V**), with isomer **IV** again in greater amount[17] (see **Scheme IX**). These two reactions are interesting since most ionic reactions with norbornadiene (**I**) result in predominately the nortricyclyl adduct, due to a facile homoallylic rearrangement.[17,18,19]

The addition of hydrogen halides to norbornadiene gives two isomers, suggesting certain intermediates. When a haloacid is added to norbornadiene, it protonates one of the double bonds to form a carbocation intermediate. Experimental results (product composition determinations) suggest that the cation is not localized on just one carbon atom. Three cationic intermediates are proposed and are shown in **Scheme X**. A method by which these carbocations can be visualized is presented in **Schemes XI** through **XIII**. First, the norbornadiene molecule (**I**) is protonated to give the carbocation **VI**a (**Scheme XI**). Next (**Scheme XII**), the π-electrons in the double bond of **VI**a can shift to create a sigma bond between positions 2 and 6 (**VI**b),

Scheme VIII

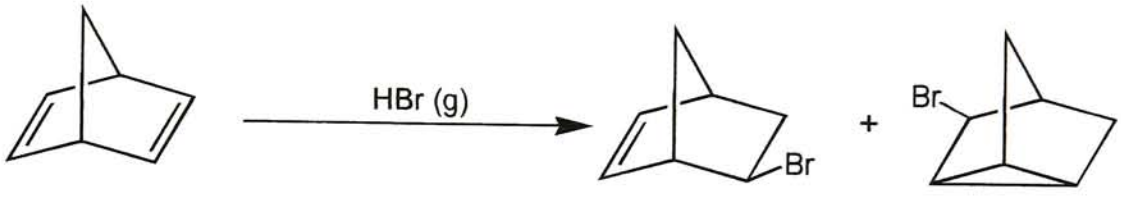


I

II
(~80%)

III
(~20%)

Scheme IX

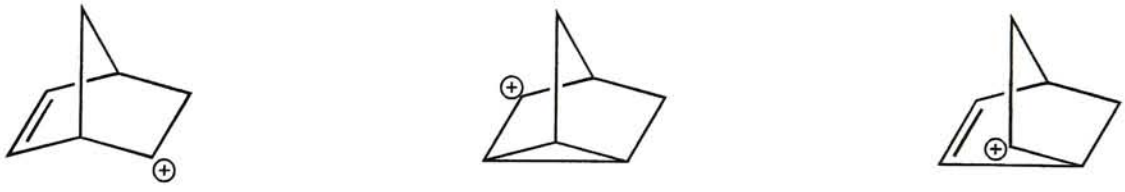


I

IV
(75%)

V
(25%)

Scheme X

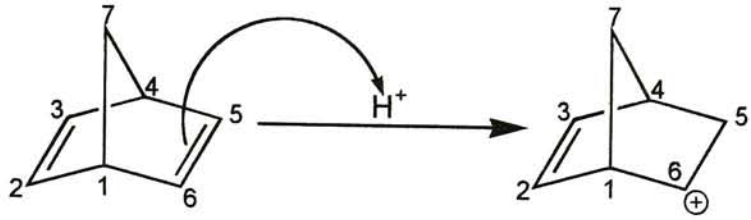


VIa

VIb

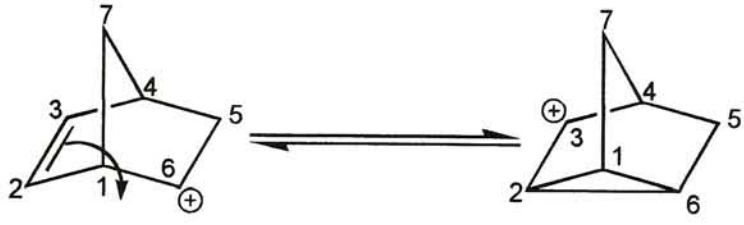
VIc

Scheme XI



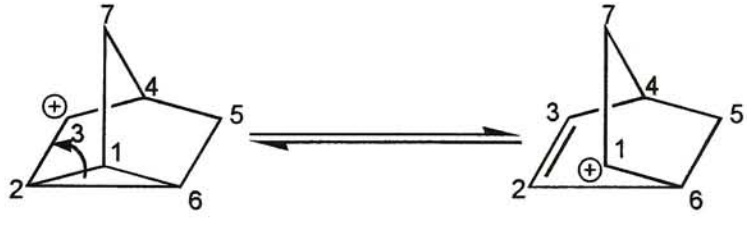
I **VIa**

Scheme XII



VIa **VIb**

Scheme XIII



VIb **VIc**

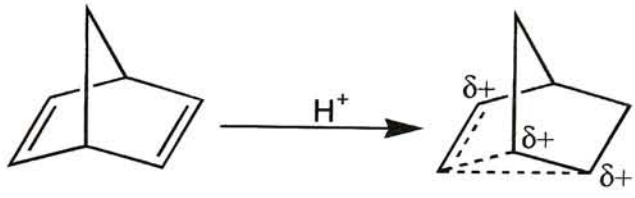
leaving a positive charge on position 3. The electron pair making up the 1,2 sigma bond in **VI**b can then migrate

(**Scheme XIII**), creating a double bond between positions 2 and 3; this results in a positive charge on position 1 (**VI**c). The net result of this movement of electron pairs is a carbocation delocalized over three carbon atoms, assuming **VI**a, **VI**b, and **VI**c are resonance forms.

A major issue in the foregoing is that of timing. Are intermediates **VI**a, **VI**b, **VI**c formed sequentially, or are they merely resonance forms of a single intermediate? If the latter is the case, the way of writing the carbocation intermediate is as a bridged ion (**Scheme XIV**). Intermediate **VI** has a partial positive charge on three carbons, and a negatively charged group such as chlorine or bromine can add nucleophilically to any one of the three positions. Evidence for the positive charge on the three positions arises from the experiment in which deuterium chloride is bubbled into a solution containing norbornadiene.[1] Analysis of the products reveals three isomers (**Scheme XV**), corresponding to chloride attacking each one of the three possible positions of positive charge.

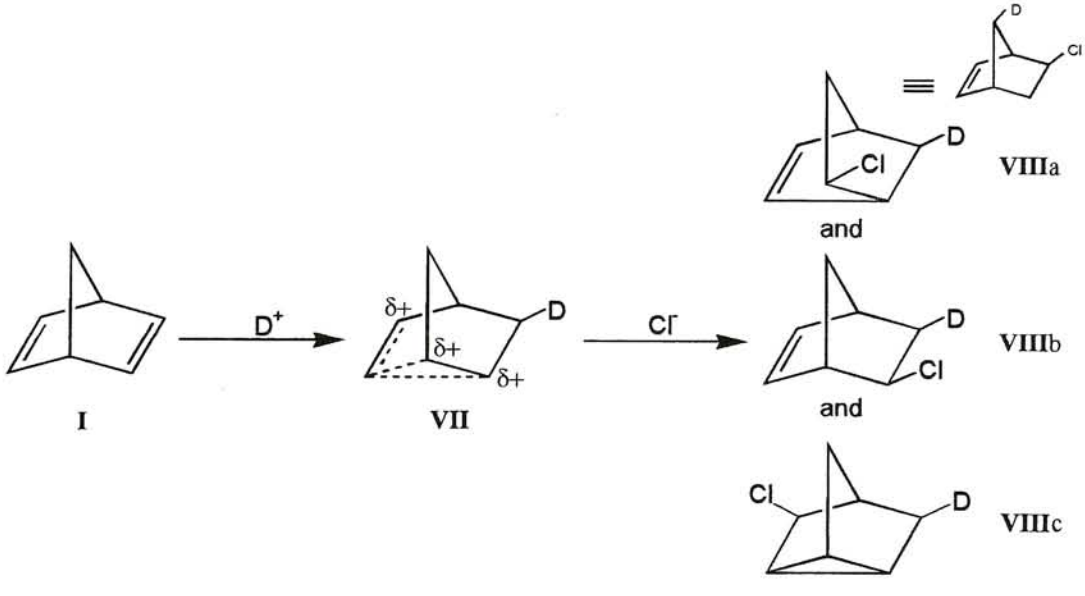
When hydrogen chloride is bubbled into a solution containing norbornadiene, a similar reaction takes place. Norbornadiene is protonated to give, for example, a delocalized carbocation intermediate, and chloride attacks the three charged positions (**Scheme XVI**). It is clear in **Scheme XVI** that two of the three isomers (**II** and **II**a) obtained are merely enantiomers of exo-5-chloronorbornene (**Scheme XVII**).

Scheme XIV

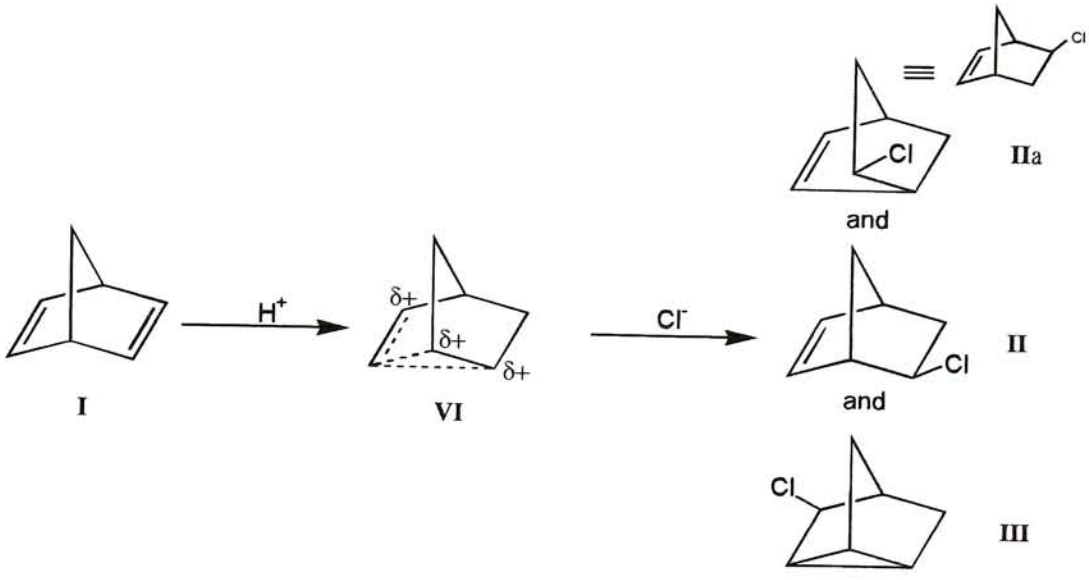


I VI

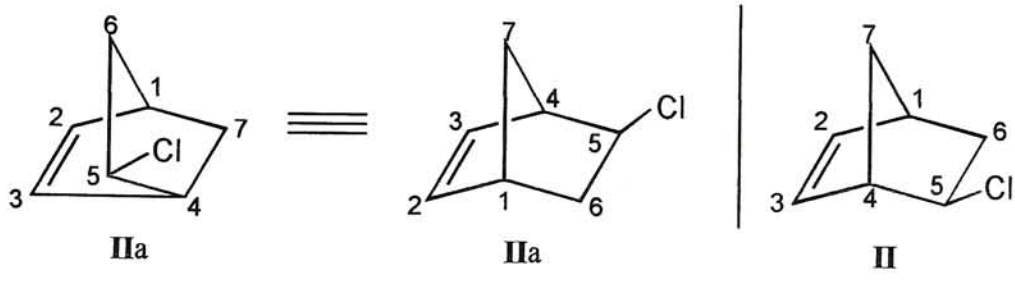
Scheme XV



Scheme XVI

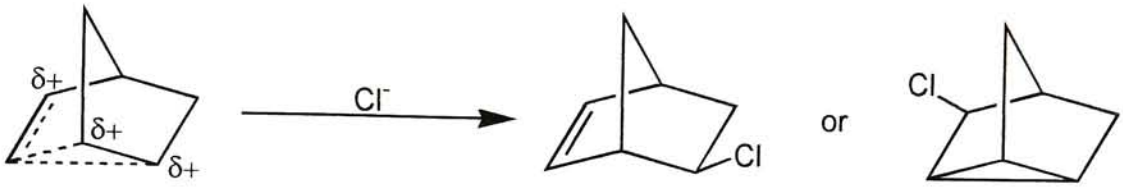


Scheme XVII

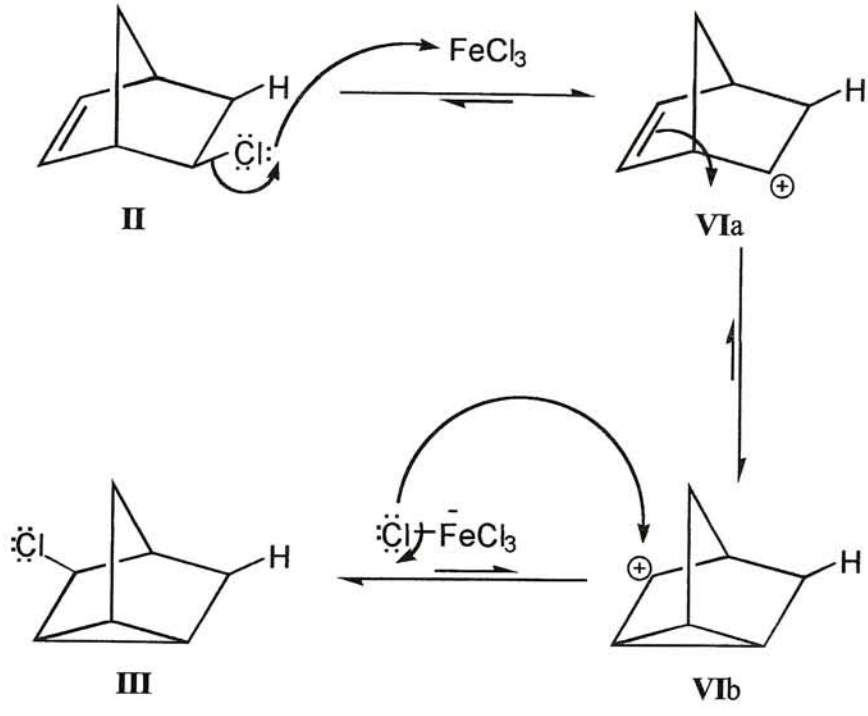


IIa IIa II

Scheme XVIII



Scheme XIX



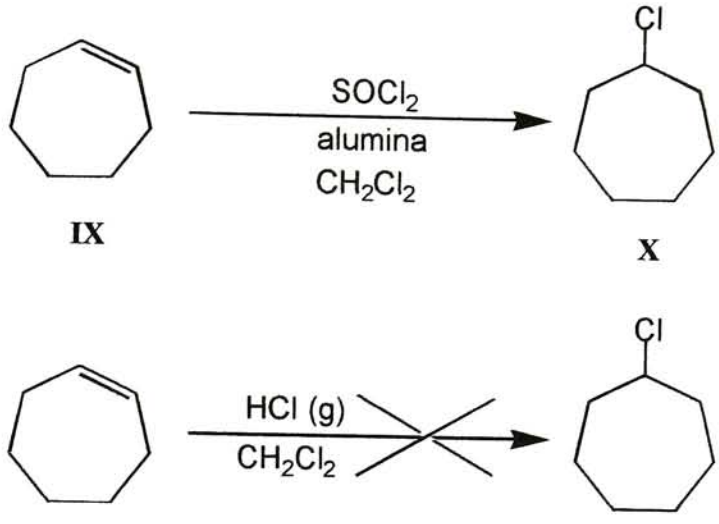
Thus, only two products are observed when hydrochlorination of norbornadiene is carried out (**Scheme XVIII** and **Scheme VIII**) and analyzed by gas chromatography.

When the products obtained from **Scheme VIII** are heated with anhydrous ferric chloride, most of the norbornenyl adduct is converted to the nortricyclyl adduct in a ratio of 5% **II** / 95% **III**.[17] This suggests that the thermodynamically more stable compound is the nortricyclyl compound (**III**). We propose that the olefinic chloride (**II**), the predominate product in the earlier HCl addition and in our alumina promoted reaction below, is the kinetic product. **Scheme XIX** rationalizes the thermodynamic control equilibrium process.

Even though hydrochlorination and hydrobromination of double bonds have been done in the past using gaseous HCl and HBr, respectively, there are many problems associated with this method. Gaseous hydrogen halides are toxic and corrosive, so special caution must be taken in handling these compounds. In addition to this, gases are generally much harder to handle than solids and liquids. Finally, alkenes do not readily undergo HCl additions unless the hydrocarbon is either highly strained or substituted such that very stable carbocations are formed.

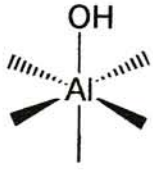
An easier way to hydrochlorinate a double bond is to use alumina or silica gel and a chlorinating agent, such as thionyl chloride or oxalyl chloride. It has been found that alumina mixed with thionyl chloride converts cycloheptene (**IX**) to chlorocycloheptane (**X**), while hydrogen chloride undergoes no detectable reaction with cycloheptane under otherwise identical conditions (both reactions run for one

Scheme XX

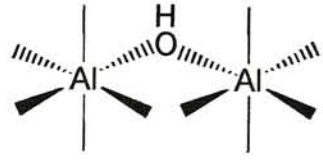


Scheme XXI

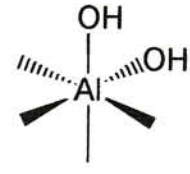
octahedral:



XIa

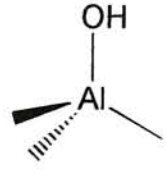


XIb



XIc

tetrahedral:



XId

hour at room temperature, **Scheme XX**) after one hour at room temperature[21] (**Scheme XX**).

Alumina is a polymeric compound composed of a network of aluminum-oxygen bonds. In the presence of atmospheric moisture, hydroxyl groups are formed on the surface, due to absorbed water. The number of hydroxyl groups is dependent upon the temperature and humidity of the atmosphere over the stored alumina.[20]

The surface of γ-alumina can have any one of four structures.[21] When alumina is octahedral (**Scheme XXI**): one hydroxyl group can be coordinated to one octahedral cation (**XI**a), one hydroxyl group can bridge two octahedral cations (**XI**b), or two hydroxyl groups can be coordinated to the same octahedral cation in a geminal arrangement (**XI**c). If the alumina is tetrahedral, only one hydroxyl group can be coordinated to each aluminum atom (**XI**d).

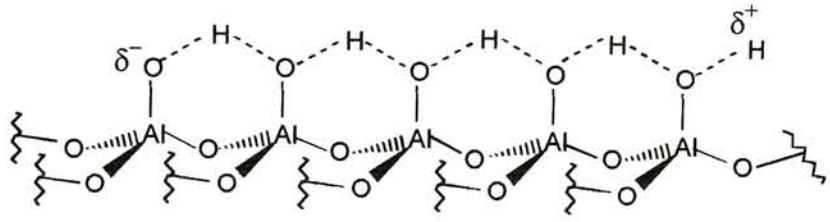
When the alumina is allowed to equilibrate with atmospheric moisture for at least 48 hours at 120°C, a larger proportion of the aluminum atoms are tetrahedrally coordinated (**XI**d). When several tetrahedrally coordinated aluminum atoms are adjacent, the hydroxyl groups mutually share hydrogens (**XII**a in **Scheme XXII**). Heating alumina higher than 120°C increases dehydration, thus decreasing the number of hydroxyl groups (**XII**b in **Scheme XXII**). Addition of hydrogen chloride to alumina results in a chlorine-aluminum bonded, and a hydroxyl group bonded to the adjacent aluminum atom[22] (**XII**c in **Scheme XXII**). This makes the unshared

hydrogen on the hydroxyl group (on the right side **XIIc** in **Scheme XXII**) acidic. The highly acidic proton on the surface of the catalyst bonds directly with a hydrogen chloride molecule (**XIId** in **Scheme XXII**) and polarizes the hydrogen chloride bond to produce a highly electrophilic proton. This proton adds to the double bond of the heptene molecule to create a carbocation (**XIIe** in **Scheme XXII**). Compounds prone to undergo reactions via cations have done so, supporting this mechanism.

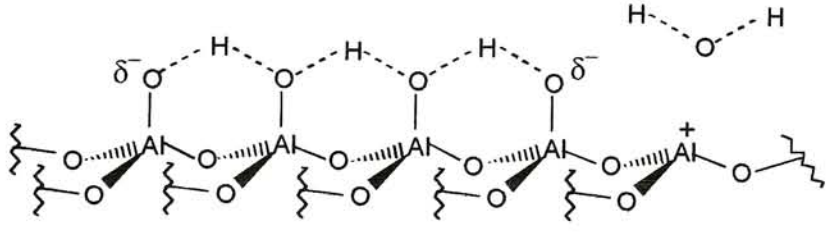
The chloride ion remaining on the surface of the catalyst has only a weak attraction to the hydroxyl group and thus a relatively high affinity for the carbocation, and thus alkyl chloride is formed quickly (**XIIf** in **Scheme XXII**). The product is a hydrochlorinated analog of the unsaturated starting material; in this case, chlorocycloheptane (**XIIg** in **Scheme XXII**).

It has been seen that alumina favors a syn HCl addition over an anti additon (**Scheme XXIII**).[20] 1,2-dimethylcyclohexene (**XIII**), in the presence of thionyl chloride and alumina, initially gives (E)-1-chloro-1,2-dimethylcyclohexane (**XIIIa**) as the major product and (Z)-1-chloro-1,2-dimethylcyclohexane (**XIIIb**) as the minor product. The reaction favors *syn*-addition due to the rapid addition of the chloride ion to the intermediate. Once the alkene is protonated, the chloride ion is added before the alkene has time to rotate to allow *anti*-addition.

Scheme XXII

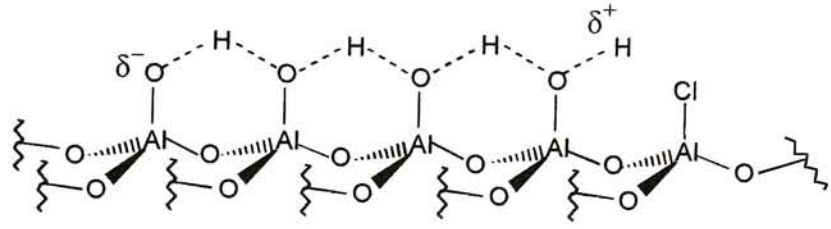


XIIa

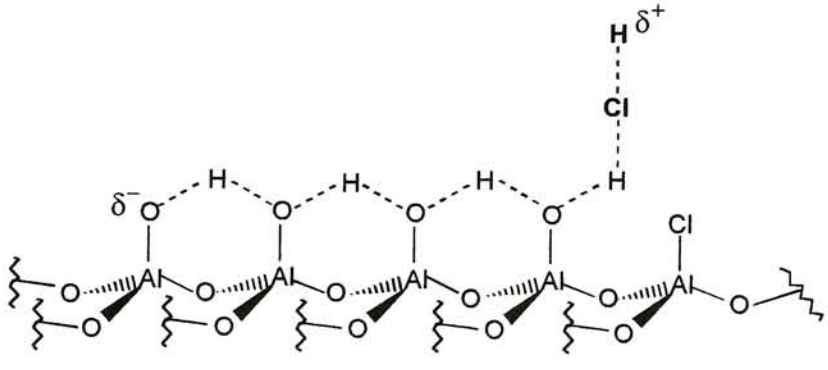


XIIb

Scheme XXII (continued)

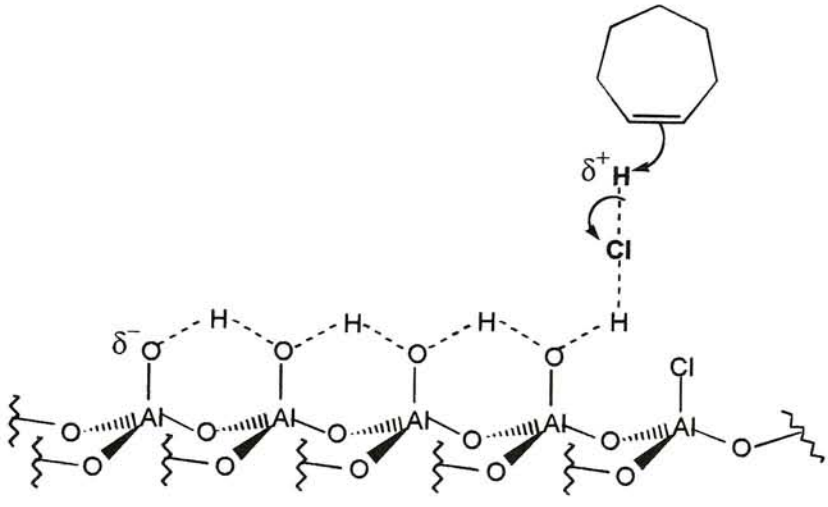


XIIc



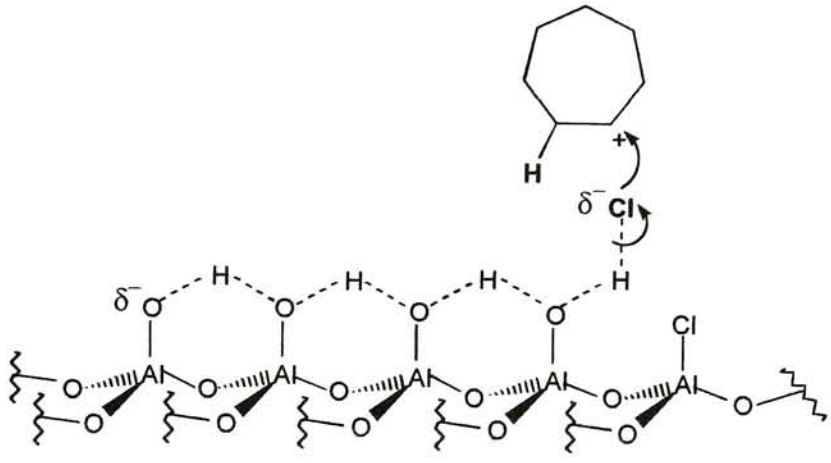
XIId

Scheme XXII (continued)

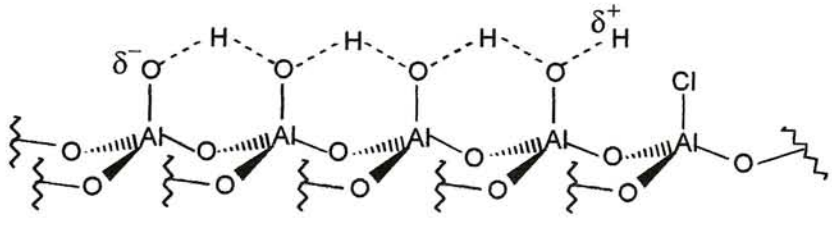


XIIe

Scheme XXII (continued)

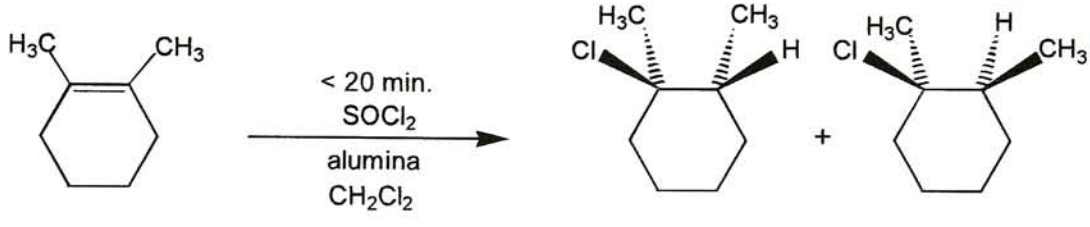


XIIf



XIIg

Scheme XXIII



XIII **XIIIa** **XIIIb**

Experimental

General. Chemicals used were supplied by the following companies: Aldrich Chemical Company, Milwaukee, WI; Sigma Chemical Company, St. Louis, MO; Fisher Scientific, Pittsburg, PA; J. T. Baker, Phillipsburg, NJ.

Standard preparative-scale hydrochlorination reaction. 30 g of 80-200 mesh alumina (Fisher, cat# A540), which had been equilibrated with the atmospheric moisture at 120°C for at least 48 hours, was placed into a 500 ml round-bottomed flask. After the contents of the flask had cooled, 250 ml of methylene chloride (J. T. Baker, cat# 9324-01) and 0.05 mole (~4.6 g) of bicyclo[2.2.1]heptadiene {norbornadiene}(Aldrich, cat# B3,380-3) was added. While the mixture was being stirred with a magnetic stirrer at room temperature, the reaction was started by adding 0.10 mole (~12.0 g) of thionyl chloride (Aldrich, cat# 23,046-4).

After 60 minutes, the methylene chloride solution was decanted from the alumina, and the alumina was washed with an additional 75 ml of methylene chloride and combined with the mother liquid. Any residual alumina in the methylene chloride solution was removed through gravity filtration with filter paper (Whatman, cat# 1001 125). The solution was washed four times with 500 ml of 1M aqueous sodium carbonate (Aldrich, cat# 22,353-0) solution, dried with anhydrous sodium

sulfate (J. T. Baker, cat# 3898-01), and then gravity filtered. BHT { butylated hydroxy toluene }(Aldrich, cat# 24,002-8) was added (1% wt/wt) to keep the sample from polymerizing, and the mixture was analyzed by gas chromatography after the methylene chloride solvent has been removed by rotary evaporation.

Purification was done by flash chromatography using methylene chloride and 230-400 mesh Merck grade 60 silica gel (Aldrich, cat# 22,719-6). The fraction of the eluent containing the products was collected, analyzed by gas chromatography, and the solvent was removed through rotary evaporation. BHT was readded (1% wt/wt), and distillation gave a clear, uncontaminated mixture of ~71% exo-5-chloronorbornene and ~29% 3-chloronortricyclene. The final mixture was found to have a shelf-life of 2-4 weeks without BHT, before it started to yellow.

Analyzing samples by gas chromatography. A Hewlett Packard 5890 capillary gas chromatograph with a FID detector and HP-5 (Crosslinked 5% Ph Me Silicone, 30 m x 0.25 mm x 0.25 μm film thickness) column was used. The helium flow rate was 1.0 ml/min, detector and injector temperatures were 280°C, oven temperature was 100°C, and the sample injection volume was 1.0 μl. After each run, the column temperature increased to 280°C for 15 minutes to assure that BHT was removed from the gas chromatograph. The solvent used was methylene chloride. Retention times were the following: methylene chloride 1.710 min., norbornadiene 1.998 min., exo-5-chloronorborene 3.175 min., and 3-chloronortricyclene 3.650 min.

Monitoring reaction by gas chromatography. A 1 ml aliquot of the reaction was removed and washed with four 2 ml portions of 1M aqueous sodium carbonate solution. This was the injected into the gas chromatograph using the above parameters.

Analysis of products by NMR. All spectra were obtained on a 300 Mhz Bruker NMR using $CDCl_3$ as the solvent.

Analysis of products by GC/MS. All spectra were obtained either on a Hewlett Packard 5890 or Hewlett Packard 5790, using the parameters indicated for GC analysis.

Synthesis of exo-5-chloronorbornene and 3-chloronortricyclene mixture. A mixture of 4.612g of norbornadiene and 250mL of methylene chloride were added to 30.014g of alumina (equilibrated at 120°C for 48 hours). A charge of 12.023g of thionyl chloride was added to the stirred mixutre to initiate the reaction. After 60 minutes, the methylene chloride solution was prepared according to the **standard preparative-scale procedure**. This afforded a 0.812g (12.6% yield) mixture of 70.1% exo-5-chloronorbornene and 29.9% 3-chloronortricyclene. Analysis by GC/MS and ^1H NMR supported these structures.

Synthesis of exo,anti-5-chlorobicyclo[2.2.1]hept-2-ene-7-d, exo,exo-6-chlorobicyclo[2.2.1]hept-2-ene-5-d, 5-chlorotricyclo[2.2.1.$0^{2,6}$]heptane-3-d, exo-5-chloronorbornene, and 3-chloronortricyclene mixture. Approximately 100g of alumina was placed in a 900°C kiln and allowed to dehydrate. After 24 hours, the alumina was cooled in a desiccator to 150°C and to this was added 150 ml of deuterium oxide. The steps of dehydration, followed by D_2O addition, were repeated. The saturated alumina was placed in a closed system heating apparatus (**Figure XVIII**) for 2 weeks with vigorous stirring daily. Then, 30.009g of the so-treated alumina was combined with 4.614 g of norbornadiene and 250 ml of methylene chloride. The reaction was started by adding 12.018 g of thionyl chloride with stirring. After 60 minutes, the methylene chloride solution was prepared according to the standard preparative-scale procedure above. This afforded a 0.798 g (12.4% yield) mixture of 18% *exo,anti*-5-chlorobicyclo[2.2.1]hept-2-ene-7-d, 33% *exo,exo*-6-chlorobicyclo[2.2.1]hept-2-ene-5-d, 21% 5-chlorotricyclo[2.2.1.$0^{2,6}$]heptane-3-d, 20% *exo*-5-chloronorbornene, and 8% 3-chloronortricyclene, as per analysis by MS/GC.

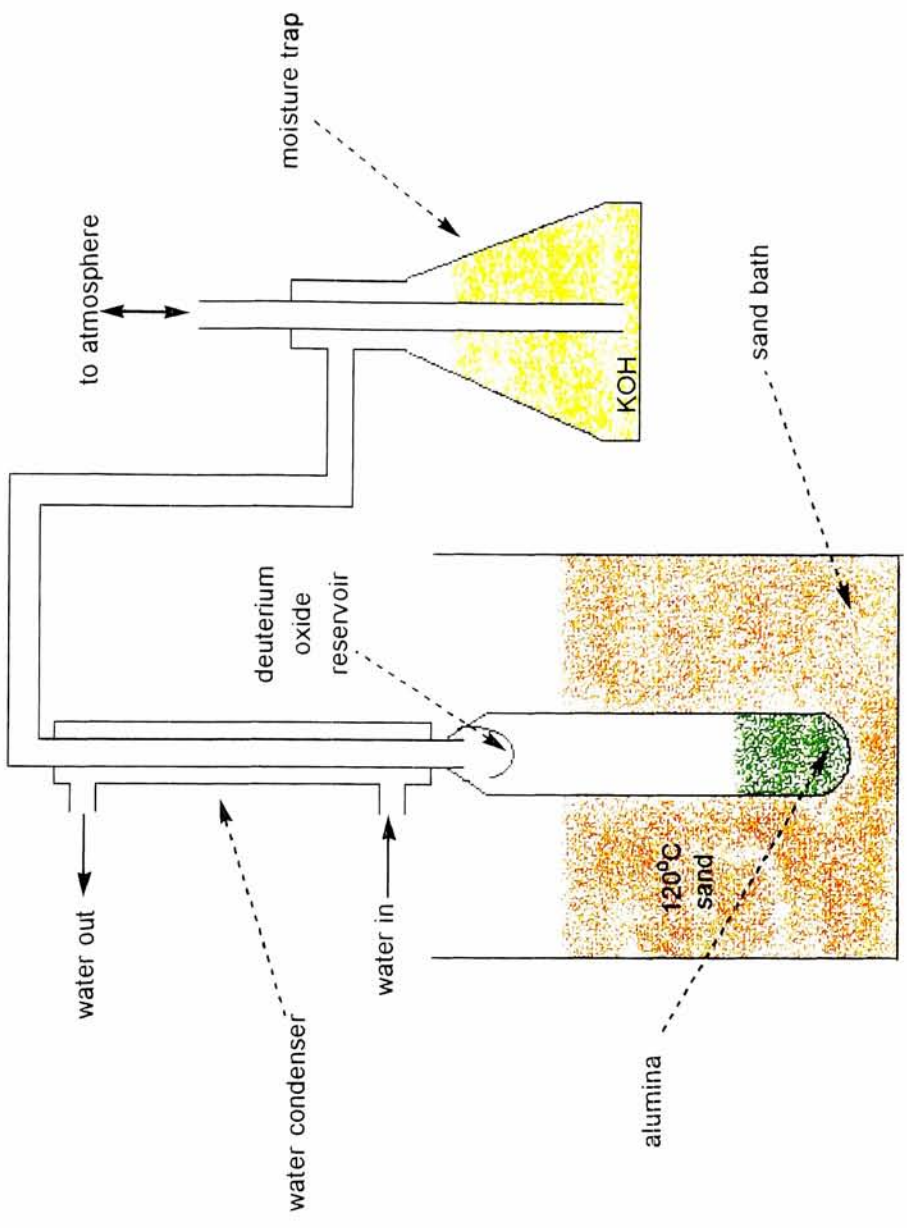


Figure XVIII: Apparatus used in the preparation of alumina with chemisorbed deuterium oxide

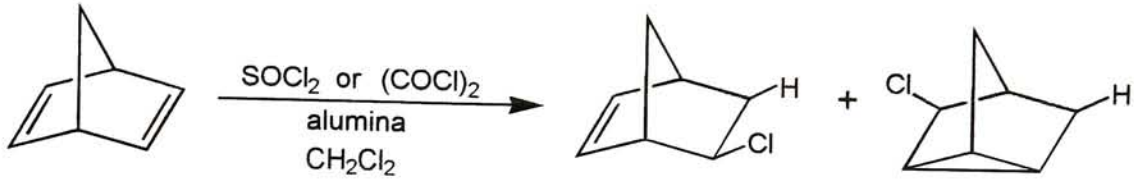
Results and Discussion

Alumina, which had been allowed to equilibrate with atmospheric moisture at 120°C for at least 48 hours, was found to promote the hydrochlorination of norbornadiene in methylene chloride when either thionyl chloride or oxalyl chloride was used (**Scheme XXIV**). Both chlorinating agents gave a mixture of exo-5-chloronorbornene (**II**) and 3-chloronortricyclene (**III**). The mass spectra and NMR of these products are shown in **Figure XIX** to **Figure XXI** . Variation in yields, product ratios, and reaction times suggest different mechanistic details for the various reactions.

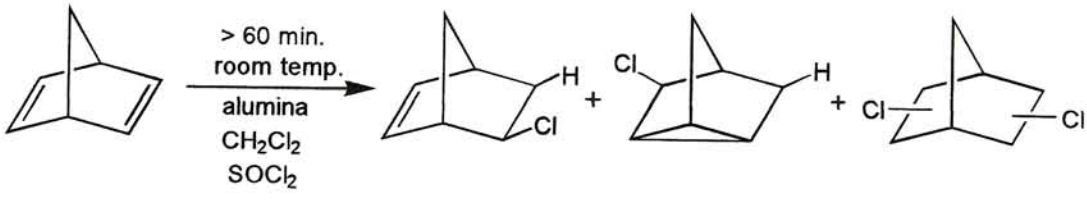
Thionyl chloride and alumina hydrochlorinate norbornadiene to give 71% (± 1%) exo-5-chloronorbornene and 29% 3-chloronortricyclene at room temperature. Virtually all of the norbornadiene had been consumed within 60 minutes, and no dichlorinated products were detected. The fact that a single hydrochlorination reaction is observed is consistent with the expectation that the first chloride atom deactivates the molecule towards a second HCl addition. It was observed, however, that extending the reaction time beyond 60 minutes resulted in three dichloro compounds (**Scheme XXV**).

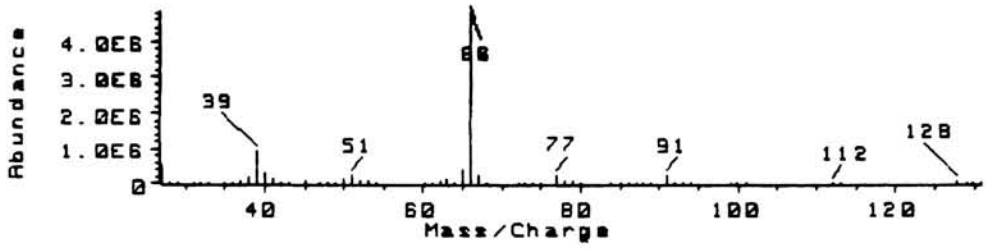
The reaction using the thionyl chloride chlorinating agent has been shown to give different ratios of the two products for various temperatures. At a constant

Scheme XXIV



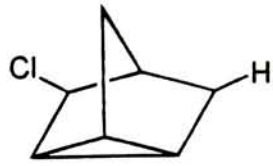
Scheme XXV

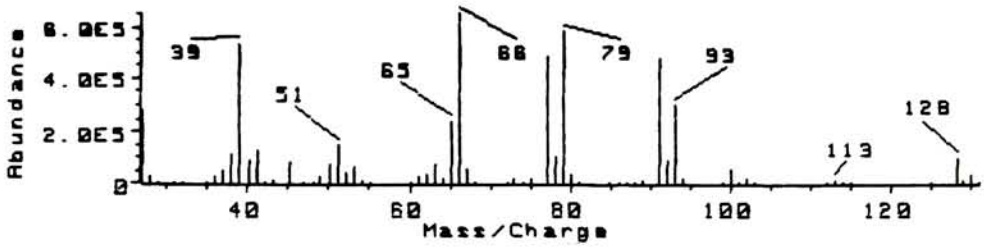




m/z	abund.	m/z	abund.
27.05	508544	66.05	4838912
28.05	40680	67.05	274240
29.05	7188	68.05	7869
31.05	6283	72.00	1673
31.85	3874	72.90	18848
32.85	1328	74.00	10576
34.95	13934	75.00	19112
35.95	33552	77.00	247424
37.05	79936	78.00	65048
38.05	204672	79.00	62624
39.05	922688	80.00	4141
40.05	291072	83.90	1986
41.05	162112	85.00	3390
42.05	6163	86.00	5612
43.05	13339	87.00	5370
45.05	56648	88.00	2225
46.95	4664	89.00	15040
47.95	5996	91.00	224448
48.95	40904	92.00	28344
50.05	133056	93.00	30096
51.05	228736	94.00	2787
52.05	66656	99.00	3994
53.05	71912	99.90	3799
54.05	7532	101.00	1866
60.05	7149	112.00	2225
61.05	36896	113.00	2055
62.05	79288	127.95	91288
63.05	126720	129.05	7348
64.05	38320	129.95	28504
65.05	427584	130.95	2302

Figure XIX : **The Mass spectrum** of *exo*-5-chloronorbornene





m/z	abund.	m/z	abund.
27.05	277952	72.00	1654
28.05	28040	72.90	17376
29.05	6674	74.00	6748
30.95	4317	75.00	18544
31.95	4317	77.00	483008
34.95	7129	78.00	99024
35.95	23312	79.00	579136
36.95	47488	80.00	37296
38.05	112168	81.00	1640
39.05	532480	84.90	2748
40.05	85536	86.00	5849
41.05	124000	87.00	5096
42.05	5996	88.00	5012
43.05	8428	89.00	11993
45.05	80584	91.00	475264
46.95	3821	92.00	84160
48.05	3810	93.00	299904
48.95	29048	94.00	21424
50.05	73288	99.00	6214
51.05	147072	100.00	54096
52.05	40240	101.00	5897
53.05	67752	102.00	18248
54.05	7288	102.90	1575
55.05	1752	112.00	3179
60.05	4365	113.00	13858
61.05	22496	114.00	2132
62.05	35904	115.00	4141
63.05	73888	124.95	1654
64.05	18904	128.05	98224
65.05	238848	128.95	8709
66.05	650624	129.95	30920
67.05	53656	130.95	2401
68.05	4862		

Figure XX : The Mass spectrum of 3-chloronortricyclene

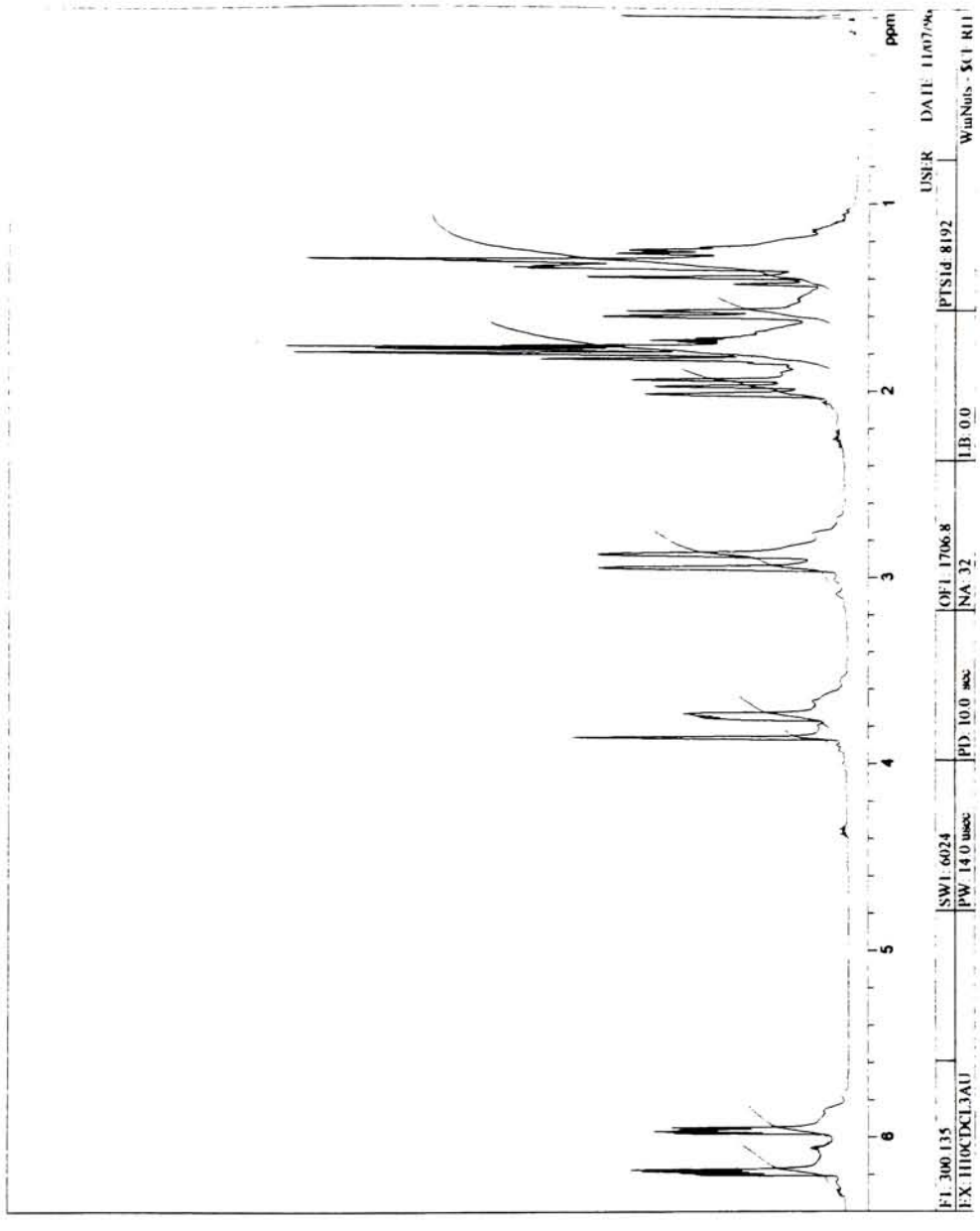


Figure XXI : The ^{1}H-NMR of 71% *exo*-5-chloronorbornene and 29% 3-chloronortricyclene in $CDCl_3$

temperature, the ratio of the products throughout the reaction remains fairly constant. Decreasing the temperature of the reaction increases the proportion of exo-5-chloronorborene in the product, and increasing the temperature increases the proportion of the 3-chloronortricyclene (**Table I**). From these results, it can be concluded that the exo-5-chloronorborene is the kinetic product. Since the product ratio is similar to that of using hydrogen chloride, the general mechanism of hydrochlorination using alumina and a chlorinating agent, as presented in **Scheme XXII**, seems valid for the thionyl chloride reaction.

Very different results were obtained when oxalyl chloride was used as the chlorinating agent (**Table II**). After a reaction time of one minute for both 26°C and 42°C, exo-5-chloronorborene is the major product. Total yield continues to increase as the reaction progresses, but the ratio of exo-5-chloronorborene to 3-chloronortricyclene decreases. At some point in the reaction between 1 and 30 minutes at 42°C, 3-chloronortricyclene became that major product. This suggests that the exo-5-chloronorborene is again the kinetically favored compound because it is initially the major product, and apparently 3-chloronortricyclene is formed by thermodynamic equilibration as the reaction progresses. Since the product ratio from the thionyl chloride reaction is constant and the oxalyl chloride reaction ratio changes, this suggests that there is a different mechanism with the two reactions. There are two possible explanations for this change in ratios, described below.

Table I: Hydrochlorination Using Thionyl Chloride

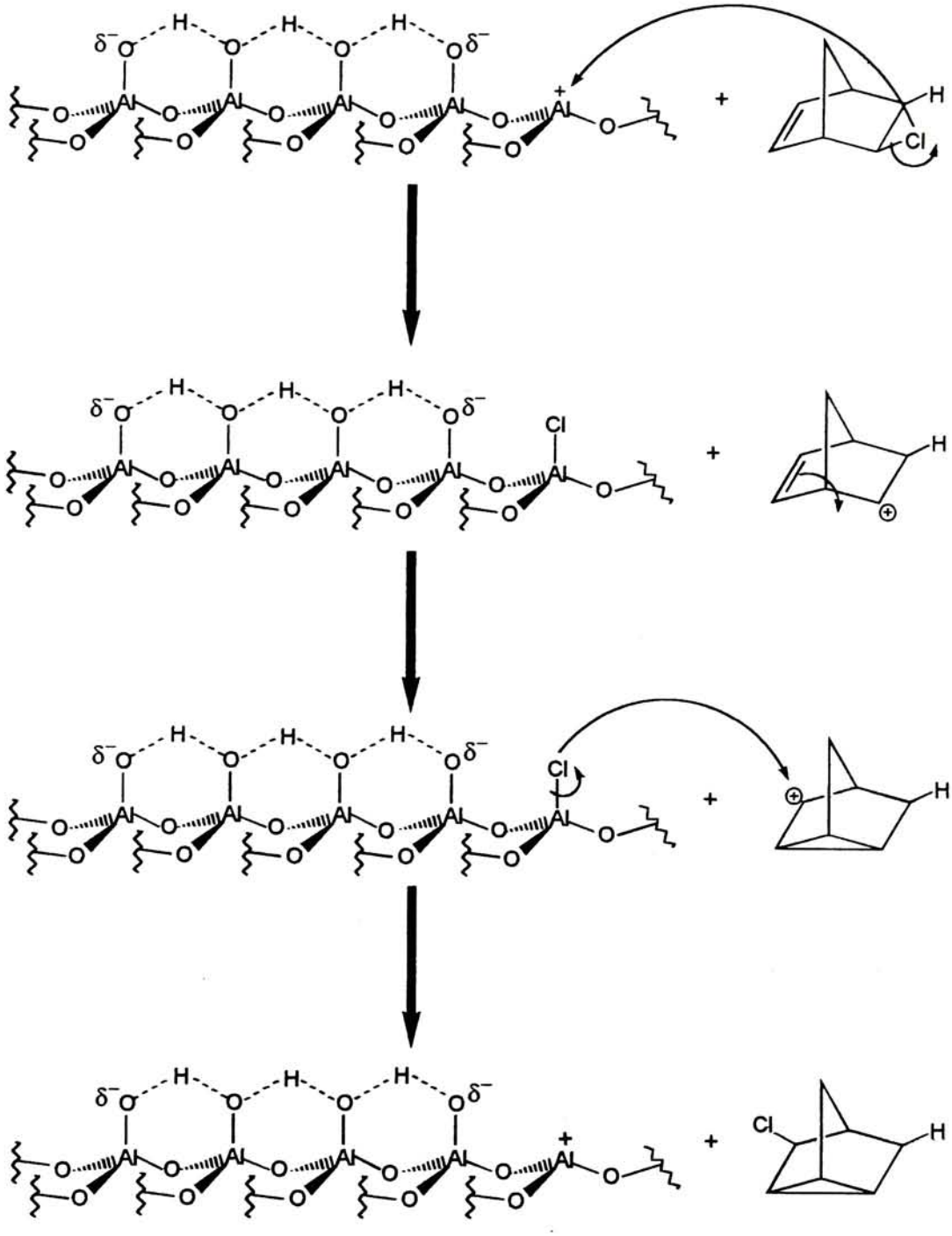
Temp(C)	Product	15 minutes		30 minutes		45 minutes		60 minutes		120 minutes		180 minutes		240 minutes	
		yield	ratio	yield	ratio	yield	ratio	yield	ratio	yield	ratio	yield	ratio	yield	ratio
42	*exo*-5chloronorbornene	*	70.3%	*	69.9%										
	3-chloronortricyclene	*	29.7%	*	30.1%										
26	*exo*-5chloronorbornene	28.4%	70.6%	33.7%	71.2%	36.7%	71.3%	38.6%	71.3%						
	3-chloronortricyclene	11.8%	29.4%	13.6%	28.8%	14.8%	28.7%	15.5%	28.7%						
-60	*exo*-5chloronorbornene			0.10%	70.9%			0.15%	73.5%	1.04%	78.2%	2.15%	79.2%	2.52%	79.7%
	3-chloronortricyclene			0.04%	29.0%			0.05%	26.5%	0.29%	21.8%	0.56%	20.7%	0.64%	20.3%

Table II: Hydrochlorination Using Oxalyl Chloride

Temp(C)	Product	1 minute		30 minutes		45 minutes		60 minutes		120 minutes		180 minutes		240 minutes	
		yield	ratio	yield	ratio	yield	ratio	yield	ratio	yield	ratio	yield	ratio	yield	ratio
42	*exo*-5chloronorbornene	26.2%	61.6%	*	33.6%			*	24.8%						
	3-chloronortricyclene	16.3%	38.4%	*	66.4%			*	75.2%						
26	*exo*-5chloronorbornene	11.3%	69.3%	29.2%	61.7%					24.3%	46.6%	22.4%	41.8%	20.4%	38.3%
	3-chloronortricyclene	5.0%	30.1%	18.1%	38.3%					27.9%	53.4%	31.2%	58.2%	32.9%	61.7%

* evaporation losses (reaction solvent) prevented yield calculation based upon solution concentrations.

Scheme XXVI



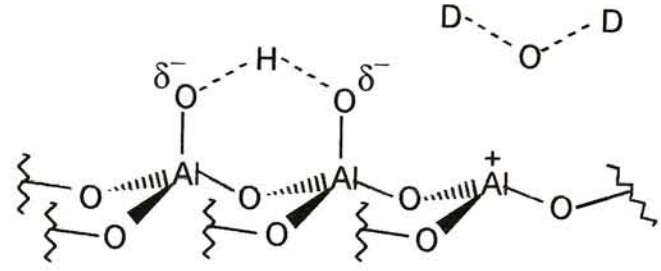
One possibility is that the surface of the alumina provides a Lewis base site to aid its rearrangement (**Scheme XXVI**). Since oxalyl chloride is a weaker chlorinating agent than thionyl chloride, the initial addition might be slow enough to allow equilibration of the olefinic compound **II** to **III**. A Lewis acidic site, such as the positively charged aluminum of **XII**g in **Scheme XXII**, could equilibrate the chloride products leading to larger amounts of 3-chloronortricyclene.

The other possiblity is that the oxalyl chloride molecule may cause the rearrangement of the products. When the oxalyl chloride is dechlorinated to form hydrogen chloride, it may be rechlorinated at the expense of the products. This would convert the product into a carbocation, and would cause the rearrangement.
In either case, the change in the ratio of the products must be cause by converting the product into a carbocation.

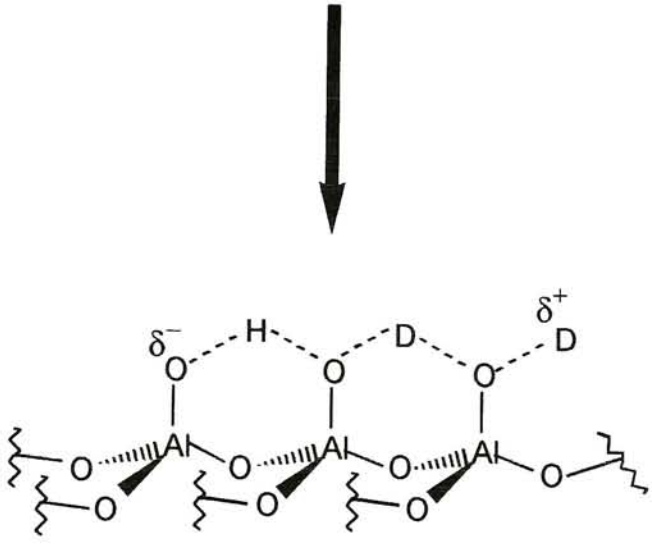
Alumina capable of promoting HCl additions possesses a chemisorbed layer of water on the surface. Removal of the water by high temperatures and treatment with deuterium oxide should result in a chemisorbed deuterium oxide layer (**Scheme XXVII**). Since HCl addition is caused by a removal of a proton from the surface of alumina to form hydrogen chloride, replacement of the protons with deuterons would cause the formation of deuterium chloride. This then leads to the useful reaction resulting from addition of DCl to norbornadiene (**I**).

Deuterated alumina and thionyl chloride in methylene chloride were found

Scheme XXVII

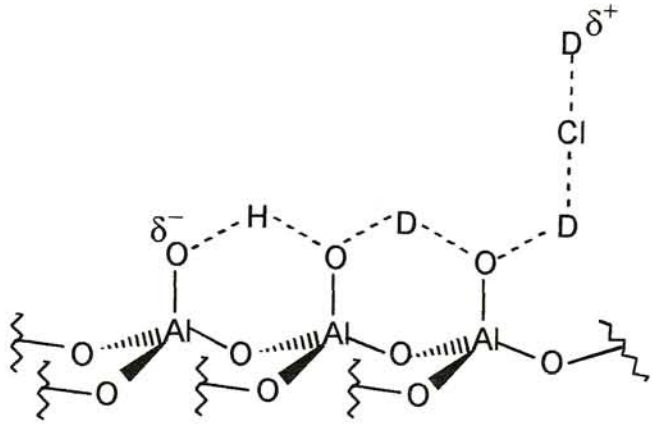


XIIIa



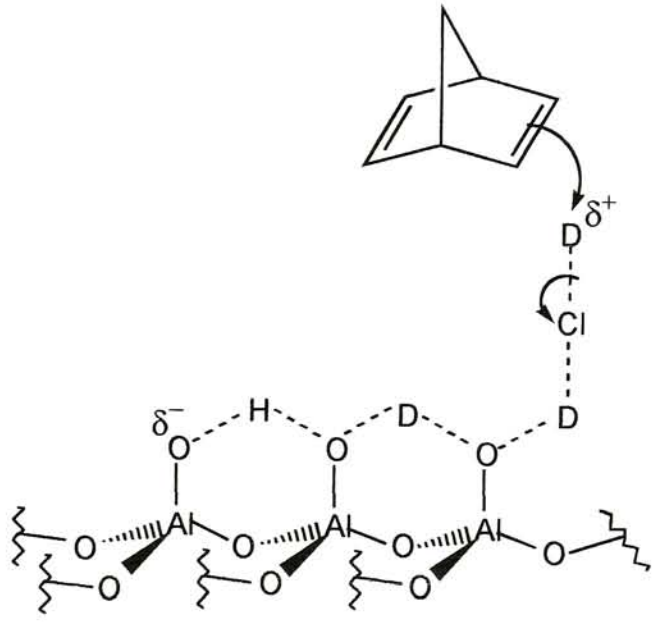
XIIIb

Scheme XXVII (continued)



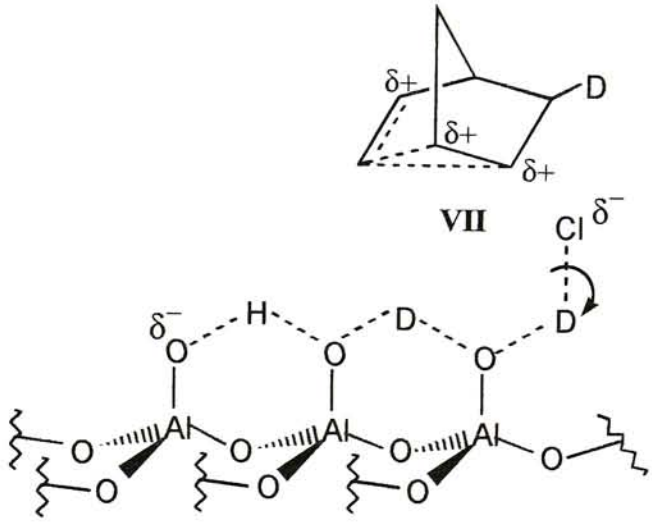
XIIIc

Scheme XXVII (continued)



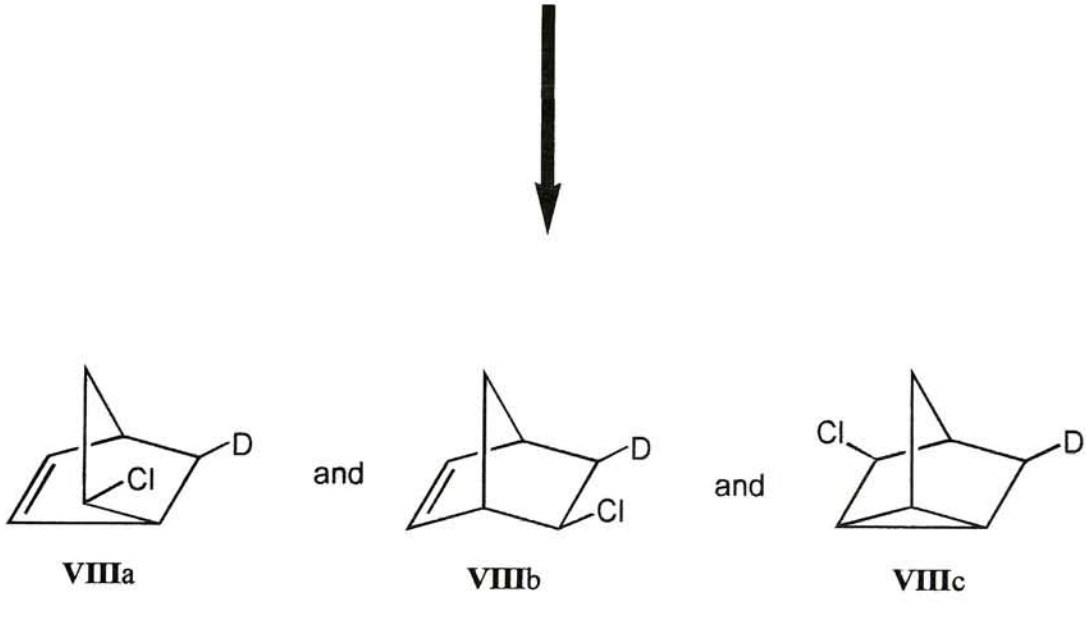
XIIId

Scheme XXVII (continued)



VII

XIIIe

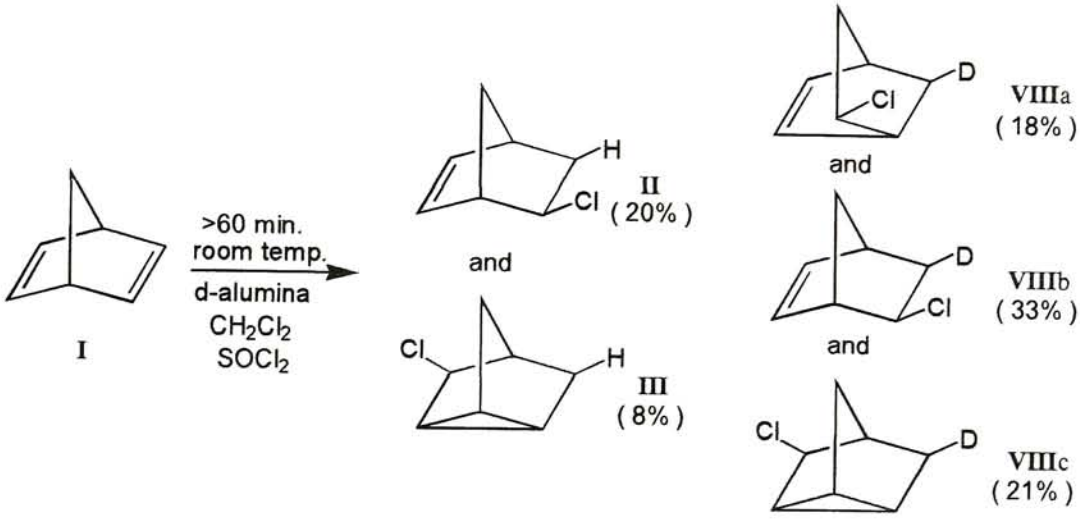


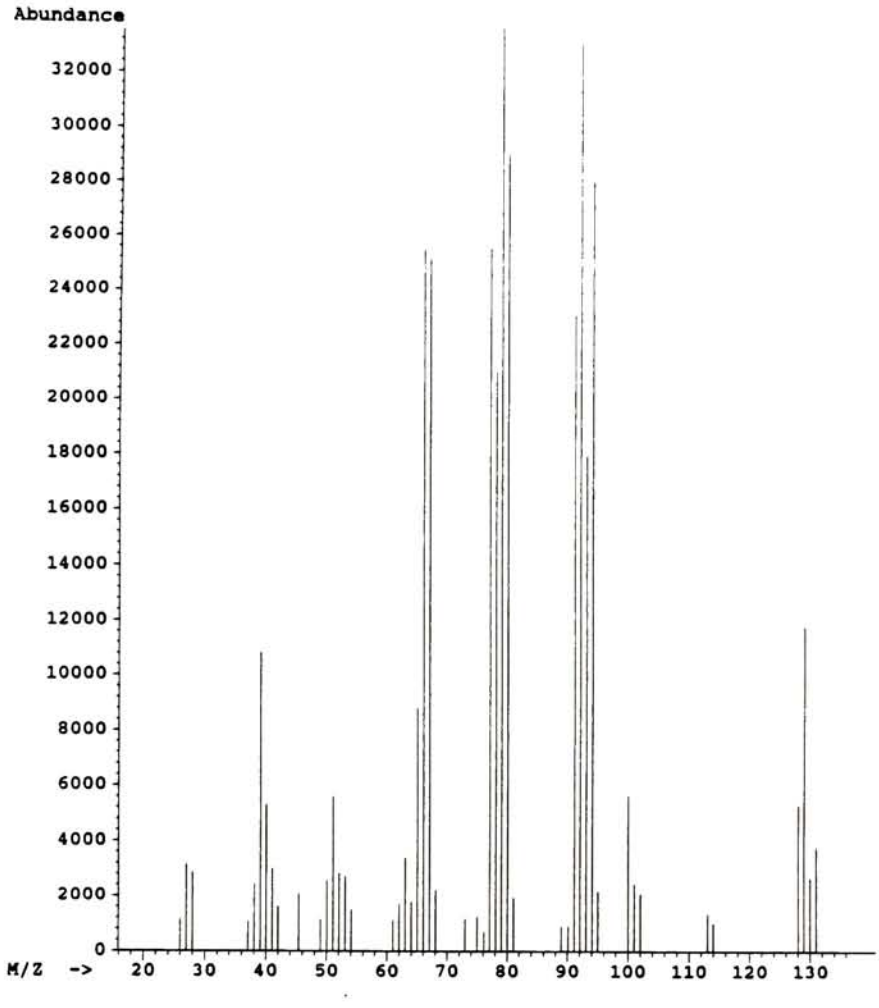
VIIIa **VIIIb** **VIIIc**

to lead to the addition of DCl to norbornadiene to form exo,anti-5-chlorobicyclo[2.2.1]hept-2-ene-7-d (**VIIIa**), exo,exo-6-chlorobicyclo[2.2.1]hept-2-ene-5-d (**VIIIb**), and 5-chlorotricyclo[2.2.1.$0^{2,6}$]heptane-3-d (**VIIIc**), as well as the undeuterated exo-5-chloronorbornene (**II**) and 3-chloronortricyclene (**III**). This is shown in **Scheme XXVIII** (GC/MS of deuterated products are shown in **Figure XXI** and **Figure XXII**). Calculations of product ratios by mass spectral data[1] showed that 73% of the products were deuterated, with 5-chlorotricyclo[2.2.1.$0^{2,6}$]heptane-3-d being the major component.

Non-catalyzed DCl addition to norbornadiene gives 43% **VIIIa** and 57% **VIIIb**,[1] while catalyzed DCl addition gives a ratio of 35.7% **VIIIa** and 64.3% **VIIIb**. The slight increase in the preference of unrearranged **VIIIb** for the catalyzed addition may be due to the rapid addition of the chloride ion after the intermediate is formed, since the **VIIIb** chloride and deuterium are closer than for **VIIIa**. Predominately syn addition was seen for various HCl catalyzed additions, possibly for the same reason.[20]

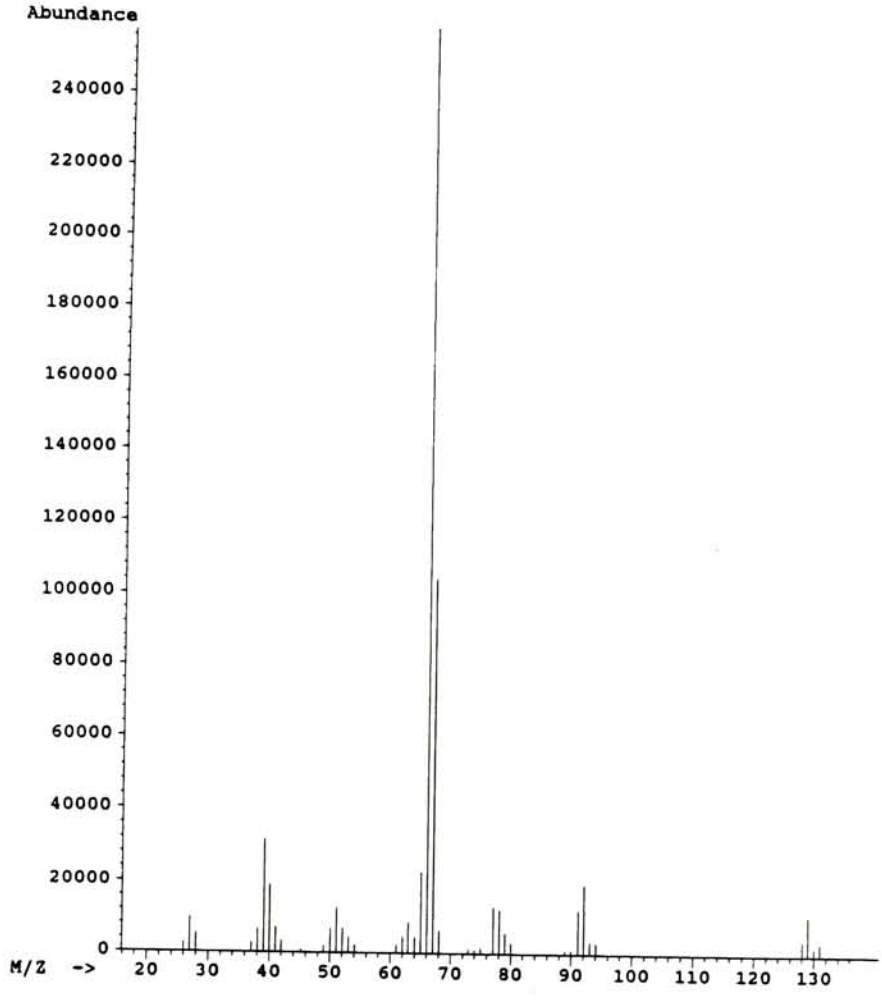
Scheme XXVIII





m/z	abund.	m/z	abund.	m/z	abund.	m/z	abund.	m/z	abund.
26.00	1178	50.05	2576	67.05	25152	90.10	915	128.05	5326
27.00	3170	51.05	5612	68.05	2212	91.10	23120	129.00	11862
28.00	2891	52.05	2842	73.00	1181	92.05	33096	130.00	2695
37.05	1091	53.05	2725	75.00	1256	93.05	18000	131.00	3799
38.05	2435	54.05	1500	76.10	702	94.05	28040		
39.05	10840	61.00	1107	77.10	25568	95.05	2187		
40.05	5296	62.00	1737	78.05	21080	100.00	5659		
41.00	3023	63.05	3418	79.05	33552	101.00	2456		
42.00	1631	64.05	1803	80.05	28968	102.00	2073		
45.40	2079	65.05	8805	81.05	1936	113.05	1367		
48.95	1144	66.05	25496	89.00	899	114.00	1031		

Figure XXII : The Mass spectrum of 25% *exo*,*anti*-5-chlorobicyclo[2.2.1]hept-2-ene-7-d, 47% *exo*,*exo*-6-chlorobicyclo[2.2.1]hept-2-ene-5-d, and 28% *exo*-5-chloronorbornene



m/z	abund.	m/z	abund.	m/z	abund.	m/z	abund.
26.00	2882	50.05	6898	67.05	104256	91.10	12358
27.00	9690	51.05	12665	68.05	6458	92.05	19480
28.00	5068	52.05	6804	73.00	1399	93.05	3554
37.05	2741	53.05	4450	74.00	1066	94.05	3233
38.05	6547	54.05	2257	75.00	1589	128.05	4084
39.05	31688	61.00	2394	77.10	13159	129.00	11140
40.05	18952	62.00	4862	78.05	12460	130.00	2126
41.00	7013	62.95	8544	79.05	5769	131.00	3524
42.00	3343	64.05	4462	80.05	3100		
45.20	960	65.05	22808	89.00	1104		
48.95	2009	66.05	257664	90.00	1147		

Figure XXIII : The Mass spectrum of 72% 5-chlorotricyclo[2.2.1.$0^{2,6}$]heptane-3-d and 28% 3-chloronortricyclene

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